


# Diagnostic performance of $^{68}\text{Ga}$ -PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients

Ali Afshar-Oromieh<sup>1,2</sup>  · Tim Holland-Letz<sup>3</sup> · Frederik L. Giesel<sup>1</sup> · Clemens Kratochwil<sup>1</sup> · Walter Mier<sup>1</sup> · Sabine Haufe<sup>1</sup> · Nils Debus<sup>1</sup> · Matthias Eder<sup>2</sup> · Michael Eisenhut<sup>4</sup> · Martin Schäfer<sup>4</sup> · Oliver Neels<sup>4</sup> · Markus Hohenfellner<sup>5</sup> · Klaus Kopka<sup>4</sup> · Hans-Ulrich Kauczor<sup>6</sup> · Jürgen Debus<sup>7</sup> · Uwe Haberkorn<sup>1,2</sup>

Received: 18 March 2017 / Accepted: 19 April 2017 / Published online: 12 May 2017  
© Springer-Verlag Berlin Heidelberg 2017

## Abstract

**Purpose** Since the clinical introduction of  $^{68}\text{Ga}$ -PSMA-11 PET/CT, this imaging method has rapidly spread and is now regarded as a significant step forward in the diagnosis of recurrent prostate cancer (PCa). The aim of this study was to analyse the influence of several variables with possible influence on PSMA ligand uptake in a large cohort.

**Methods** We performed a retrospective analysis of 1007 consecutive patients who were scanned with  $^{68}\text{Ga}$ -PSMA-11 PET/CT (1 h after injection) from January 2014 to January 2017 to detect recurrent disease. Patients with untreated primary PCa or patients referred for PSMA radioligand therapy

were excluded. The possible effects of different variables including PSA level and PSA doubling time ( $\text{PSA}_{\text{DT}}$ ), PSA velocity ( $\text{PSA}_{\text{Vel}}$ ), Gleason score (GSC, including separate analysis of GSC 7a and 7b), ongoing androgen deprivation therapy (ADT), patient age and amount of injected activity were evaluated.

**Results** In 79.5% of patients at least one lesion with characteristics suggestive of recurrent PCa was detected. A pathological (positive) PET/CT scan was associated with PSA level and ADT. GSC, amount of injected activity, patient age,  $\text{PSA}_{\text{DT}}$  and  $\text{PSA}_{\text{Vel}}$  were not associated with a positive PET/CT scan in multivariate analysis.

**Conclusion**  $^{68}\text{Ga}$ -PSMA-11 PET/CT detects tumour lesions in a high percentage of patients with recurrent PCa. Tumour detection is clearly associated with PSA level and ADT. Only a tendency for an association without statistical significance was found between higher GSC and a higher probability of a pathological PET/CT scan. No associations were found between a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan and patient age, amount of injected activity,  $\text{PSA}_{\text{DT}}$  or  $\text{PSA}_{\text{Vel}}$ .

**Electronic supplementary material** The online version of this article (doi:10.1007/s00259-017-3711-7) contains supplementary material, which is available to authorized users.

✉ Ali Afshar-Oromieh  
a.afshar@gmx.de

- <sup>1</sup> Department of Nuclear Medicine, Heidelberg University Hospital, INF 400, 69120 Heidelberg, Germany
- <sup>2</sup> Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Centre, Heidelberg, Germany
- <sup>3</sup> Department of Biostatistics, German Cancer Research Center, Heidelberg, Germany
- <sup>4</sup> Division of Radiopharmaceutical Chemistry, German Cancer Research Center, Heidelberg, Germany
- <sup>5</sup> Department of Urology, Heidelberg University Hospital, Heidelberg, Germany
- <sup>6</sup> Department of Diagnostic and Interventional Radiology, Heidelberg University Hospital, Heidelberg, Germany
- <sup>7</sup> Department of Radiation Oncology and Therapy, Heidelberg University Hospital, Heidelberg, Germany

**Keywords** Prostate cancer · PET/CT · Positron emission tomography · PSMA · Prostate-specific membrane antigen

## Introduction

Prostate cancer (PCa) is the most frequent tumour entity in men worldwide and its incidence has increased in recent years [1]. After initial curative therapy, biochemical recurrence is frequent in men with high-risk PCa. In such a constellation, searching for recurrent tumour is challenging using conventional imaging modalities such as CT and MRI due to low

sensitivity and specificity. As a consequence, there is a need for improved diagnostic tools. In this context, prostate-specific membrane antigen (PSMA) has received increased attention during recent years. PSMA is a transmembranous enzyme which is significantly overexpressed in the majority of prostatic adenocarcinomas. The level of PSMA expression rises with increasing tumour dedifferentiation, and in metastatic and hormone-refractory cancers [2–4]. Despite its name, PSMA is not specific to prostate tissue. A lower level of expression is seen in various other tissues such as brain, kidney, salivary glands, liver, ganglia and small intestine [2, 5]. Since the late 1990s, it has been known that the neovasculature of many solid tumours also expresses PSMA [5]. Recently, there have been many reports of the uptake of PSMA ligands in various nonprostate tissues [6–18].

In 2011,  $^{68}\text{Ga}$ -PSMA-11 (also known as HBED-CC, Glucurea-Lys(Ahx)-HBED-CC, and PSMA-HBED-CC) was introduced for the clinical imaging of PCa. Since then, PET using  $^{68}\text{Ga}$ -PSMA-11 has been regarded as an important step forward in the diagnosis of recurrent PCa. The first reports indicated that this novel method is significantly superior to alternative methods used for the detection of recurrent PCa [19, 20]. More recent reports have confirmed the high sensitivity and specificity of  $^{68}\text{Ga}$ -PSMA-11 PET/CT [21–24]. In addition, two studies have analysed possibly interacting factors including the level of prostate-specific antigen (PSA), PSA doubling time ( $\text{PSA}_{\text{DT}}$ ), PSA velocity ( $\text{PSA}_{\text{Vel}}$ ), Gleason score (GSC), ongoing androgen deprivation therapy (ADT), patient age and amount of injected activity in cohorts of 319 and 248 patients [21, 22]. Similar studies with smaller patient cohorts have also been reported [25, 26]. The aim of this study was to analyse a significantly larger patient cohort and compare the results with those in the existing literature.

## Materials and methods

### Patients

This was a retrospective analysis of 1007 consecutive patients who underwent PET/CT 1 h after injection of  $^{68}\text{Ga}$ -PSMA-11 between January 2014 and January 2017 in our department. The characteristics of the patients are summarized in Table 1.

Some of the data from 76 patients in the present study have been analysed in previous studies on different topics [18–20, 24–26]. Patients without recurrent disease and patients who were referred for PSMA radioligand therapy were excluded from this study. Patients with very low PSA values ( $<0.1$  ng/ml, 15 patients) were referred for  $^{68}\text{Ga}$ -PSMA-11 PET/CT if imaging with an alternative modality including CT and MRI indicated suspicion of progressive disease. To increase the validity of the statistical analysis, only the initial PET/CT scan

**Table 1** Characteristics of patients investigated in this study

Characteristic	Value
Age (years) ( $n = 1007$ )	
Mean $\pm$ SD	68 $\pm$ 7.8
Median (range)	68 (39–90)
Tracer (MBq) ( $n = 1007$ )	
Mean $\pm$ SD	227 $\pm$ 66
Median (range)	233 (66–400)
Gleason score ( $n = 864$ ; missing 143)	
Mean $\pm$ SD	8.0 $\pm$ 1.0
Median (range)	7 (5–10)
PSA at PET (ng/ml) ( $n = 971$ ; missing 36)	
Mean $\pm$ SD	12.1 $\pm$ 53.9
Median (range)	2.2 (0.01–1,237)
Prostatectomy ( $n$ )	
Yes	828
No	175
Radiation therapy ( $n$ ) <sup>a</sup>	
Yes	600
No	392
Androgen deprivation therapy at PET ( $n$ )	
Yes	221
No	680
PSA doubling time (months) ( $n = 317$ ; missing 690)	
<1	14
1–3	80
3–6	81
6–12	76
>12	66

<sup>a</sup> To the prostate gland or the prostate fossa after prostatectomy

of each patient was included in this evaluation, regardless of eventual referral for subsequent PET/CT scans.

### Radiotracer

$^{68}\text{Ga}$ -PSMA-11 was produced as previously described [21, 27]. Briefly, [ $^{68}\text{Ga}$ ]Ga<sup>3+</sup> was obtained from a  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator and used for radiolabelling PSMA-11. The  $^{68}\text{Ga}$ -PSMA-11 solution was administered to the patients as an intravenous bolus injection (mean 227  $\pm$  66 MBq, range 66–400 MBq). The target injected activity was 2 MBq per kilogram body weight. Variations in the amount of injected activity were caused by the short physical half-life of  $^{68}\text{Ga}$  (68 min), the variable elution efficiency of the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator during its life-time and unexpected delays in clinical routine.

### Imaging

The patients were investigated with two different scanners. A Biograph-6 PET/CT scanner was used until August 2015 and

was then replaced by a Biograph mCT Flow scanner (both Siemens, Erlangen, Germany). The two PET/CT scanners were cross-calibrated.

The scan protocol for the Biograph-6 scanner (whole-body 1 h after injection, whole-body or part-body 3 h after injection) was as described previously [21]. For the Biograph mCT Flow scanner, a whole body CT scan without contrast enhancement was performed 1 h after injection with the following parameters: slice thickness 5 mm, increment 3–4 mm, soft tissue reconstruction kernel, and CARE Dose. Immediately after CT scanning, a PET scan was acquired in three dimensions (matrix  $200 \times 200$ ) in flow motion at 0.7 cm/min. The emission data were corrected for randoms, scatter and decay. Images were reconstructed with an ordered subsets expectation maximization algorithm with two iterations and 21 subsets and with gaussian filtering to a transaxial resolution of 5 mm at full-width at half-maximum. Attenuation correction was performed using the low-dose non-enhanced CT data. The PET and CT scans were performed using the same protocol in every patient on the Biograph mCT Flow scanner.

All patients were asked to drink 1 l of water 30 min after tracer injection. No diuretics were administered between tracer injection and the acquisition 1 h after injection. Immediately prior to the scans, patients were asked to empty their urinary bladder. There were no special requirements regarding diet, sobriety or pausing ADT.

### Image analysis

All scans were first analysed by three physicians at an interdisciplinary conference consisting of a board-certified nuclear medicine physician, an assistant nuclear medicine physician and an assistant radiology physician supported by a board-certified radiology physician. The reports were later validated by the head of both departments or alternatively by their representatives (all board-certified physicians). Thereafter, all reports were saved and stored.

### Lesion evaluation

All lesions considered visually typical of PCa were counted and analysed unless the patient presented with disseminated metastases. In patients with nondisseminated metastases, all lesions were analysed with regard to type (lymph node, bone metastases, local relapse or soft tissue metastases), their location and their maximum standardized uptake value (SUVmax), as this is common in our clinical routine.

### Statistical analysis

For statistical analysis, Excel 2010 (Microsoft, Redmond, WA), Sigmaplot version 13 software (Systat Software Inc., WA) and R version 3.3.2 were used. In all cases a *p* value of

<0.05 was considered statistically significant. The following statistical analyses were used:

1. In the primary analysis, the associations between positive (pathological) PET/CT results and the following variables were investigated in both a univariate and a multivariate logistic regression analysis: hormonal therapy (at the time of PET/CT), patient age, amount of injected activity, PSA level and initial GSC.
  - GSC was analysed using two different approaches: (a)  $GSC \leq 7a$  versus  $\geq 7b$  analysed as categorical variables (primary analysis); (b) four different classes: GSC 5/6 (as reference against which all other classes were compared), GSC 7 (including both 7a and 7b), GSC 8, and GSC 9/10.
  - The amount of injected tracer activity was analysed as multiples of 50 MBq. The odds ratios therefore refer to increments of 50 MBq.
  - Patient age was analysed as multiples of 10 years.
  - PSA levels showed a skewed distribution and were therefore converted to a natural logarithmic scale (log PSA).
2. The associations between positive (pathological) PET/CT results and  $PSA_{DT}$  and  $PSA_{Vel}$  were also investigated using an extension of the multivariate logistic regression model from the primary analysis. As these variables were only available for a small proportion of the patients, both  $PSA_{DT}$  and  $PSA_{Vel}$  were investigated in two separate supplementary analyses based on a smaller group of patients for whom all variables were available. In both cases,  $PSA_{DT}$  and  $PSA_{Vel}$  were primarily coded as continuous variables. For the first analysis, only  $PSA_{DT}$  was added to the multivariate model. For the second analysis, both  $PSA_{DT}$  and  $PSA_{Vel}$  were added to the model.
 

As an additional sensitivity analysis,  $PSA_{DT}$  was also classified into five different classes: up to 1 month (as reference against which all other classes were compared), 1–3 months, 3–6 months, 6–12 months, and >1 year.
3. The proportions of positive PET results were calculated for subgroups defined according to PSA levels and GSC. Exact binomial 95% confidence intervals were determined for these estimates.

A patient-based sensitivity analysis was also performed. However, patient-based calculation of specificity, negative predictive value and positive predictive value was not possible as we assumed that all patients had recurrent disease and therefore the cohort did not include true-negative cases.

To provide an individualized calculation of the probability of a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan at 1 h after

injection, a Microsoft-Excel file was created and is attached to the supplementary data of this article (Supplementary File 1). By inserting individual patient parameter values (age, ADT, PSA level and GSC), the percentage of patients with a pathological scan can be calculated. To strengthen the statistical validity of the calculation, we excluded  $PSA_{DT}$  and  $PSA_{Vel}$  as otherwise the numbers of patients in the database in whom all variables were available would have decreased from 755 to 260 (including  $PSA_{DT}$ ) and 61 (including  $PSA_{Vel}$ ). However, it has to be emphasized that the values calculated are only approximate, and no warranty can be given for the calculated ratios and percentages.

## Results

In none of the patients were any adverse or clinically detectable pharmacological effects following injection of the radiotracer detected. According to information provided by the patients, 277 had previous surgical therapy only, 110 had previous radiation therapy only, 14 had ADT only, none had chemotherapy only, 337 had surgery and additional radiation therapy, 111 had surgery, radiation therapy and ADT, 9 had surgery, radiation therapy, ADT and chemotherapy, and 5 had surgery, radiation therapy and chemotherapy. Fourteen patients were pretreated with high-intensity focused ultrasound.

In 801 of the 1007 patients (79.5%) at least one lesion characteristic of recurrent PCa was detected on  $^{68}\text{Ga}$ -PSMA-11 PET/CT. The patient-based sensitivity was therefore 79.5% with a 95% confidence interval of 77.0% to 81.9%. The rates (including confidence intervals) of pathological PET/CT scans in relation to PSA levels and GSC are presented in Figs. 1 and 2, respectively.

Supplementary File 2 includes a list of the lesion sites in the 801 PET-positive patients. These patients include those with exclusively local relapse/pretreated primary tumour ( $n = 97$ ), with exclusively lymph node metastases ( $n = 154$ ), with exclusively bone metastases ( $n = 18$ ), with exclusively visceral metastases (including pelvic fat tissue or organ metastases,  $n = 6$ ), and with lymph node and bone metastases ( $n = 113$ ).

$PSA_{DT}$  was available in 317 patients: up to 1 month in 14 patients, 1–3 months in 80, 3–6 months in 81, 6–12 months in 76 and >1 year in 66. Mean calculated  $PSA_{DT}$  was  $337 \pm 719$  days (range 7–7737 days, median 165 days).  $PSA_{Vel}$  was available in 69 patients (mean  $PSA_{Vel}$   $29.1 \pm 54.4$  ng/ml per year, range 0.6–160.7 ng/ml per year, median of 7.8 ng/ml per year). The 801 patients with pathological radiotracer uptake had a median PSA level of 2.8 ng/ml (range 0.01–1237 ng/ml) and a median GSC of 7.0 (range 5–10), and were injected with a mean activity of 227 MBq  $^{68}\text{Ga}$ -PSMA-11 (range 66–380 MBq, median 233 MBq). The 206 patients without pathological findings had a median PSA level of 2.4 ng/ml (range 0.01–127 ng/ml) and a median GSC

of 7 (range 5–9), and were injected with a mean activity of  $224 \pm 66$  MBq (range 66–399 MBq, median 234 MBq).

The primary multivariate analysis of those patients in whom all variables were available ( $n = 755$ ) showed strong and significant associations between a positive PET result and log PSA level as well as ADT. No significant or relevant associations were found between a positive PET result and the following parameters: GSC, patient age or amount of injected activity. These results did not depend in a relevant way on whether GSC was included as a continuous variable (Table 2) or as a categorical variable (Table 3). The analyses including  $PSA_{DT}$  ( $n = 260$ ; Tables 4 and 5) and both  $PSA_{DT}$  and  $PSA_{Vel}$  ( $n = 61$ ; Table 6) showed no significant or relevant effects of either variable. This did not change if  $PSA_{DT}$  was included as a categorical variable.

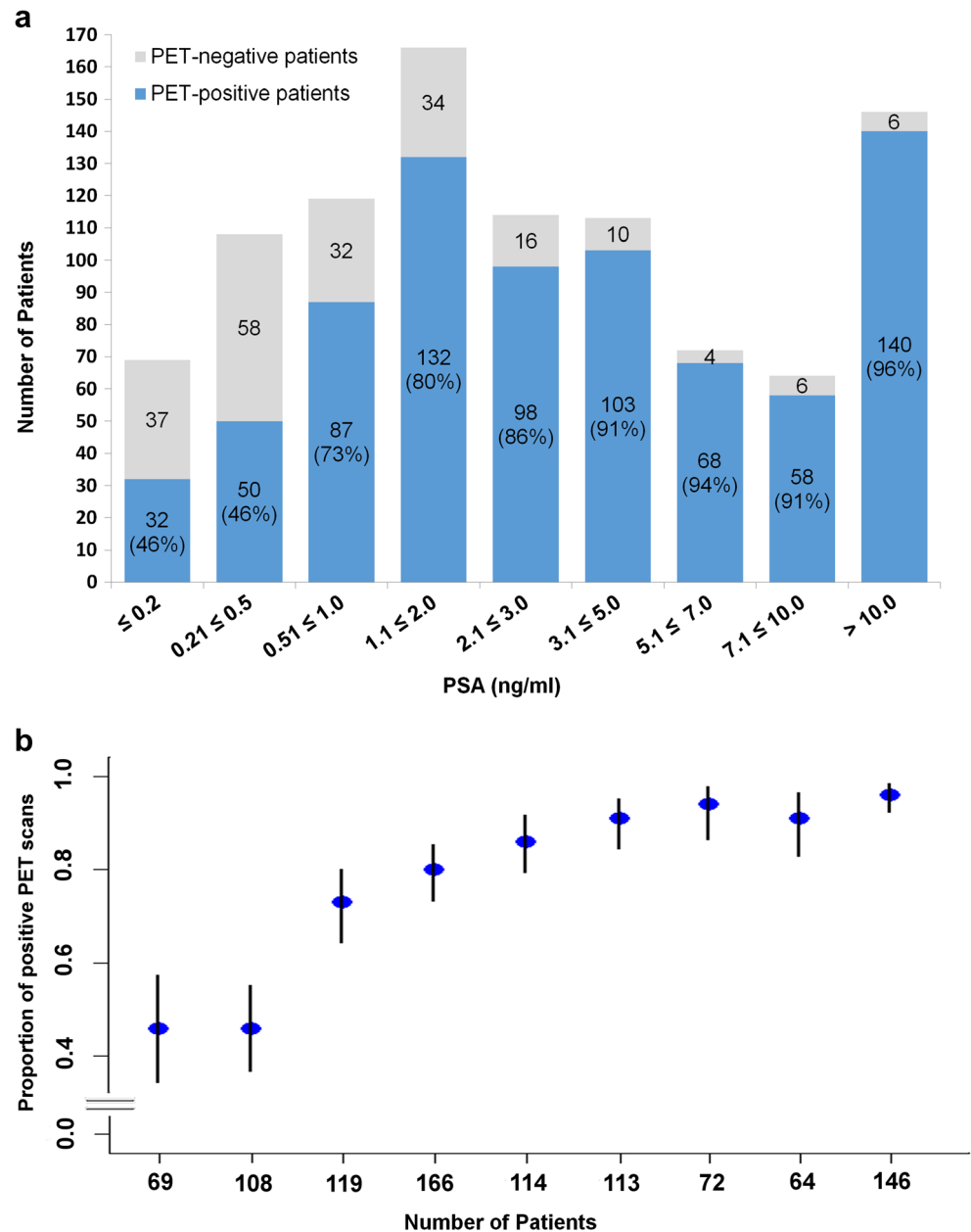
The univariate analysis showed no significant differences between PET-positive and PET-negative patients with regard to the amount of injected activity (logistic regression  $p = 0.54$ ) and GSC (logistic regression  $p = 0.78$ ). However, there were significant differences for log PSA and ADT (logistic regression  $p < 0.001$  for both). The univariate analysis demonstrated no significant effects of the variables singly. The results of the univariate analysis are presented in Supplementary Table 1.

## Discussion

Since its clinical introduction in 2011, the use of  $^{68}\text{Ga}$ -PSMA-11 PET/CT has rapidly spread. Several different PSMA ligands have also been introduced for clinical PET imaging. So far, these alternative PSMA ligands have been used in small patient cohorts only. In addition, it can be assumed that these ligands have different pharmacokinetics and sensitivities for tumour detection. The data presented here are therefore valid only for  $^{68}\text{Ga}$ -PSMA-11 PET/CT performed 1 h after injection. As mentioned above, factors that could interact with the PET/CT PSMA ligand have been analysed in two studies with patient cohorts comprising more than 200 patients as well as in studies with smaller cohorts [21, 22, 25, 26]. The aim of this study was to analyse a significantly larger cohort of patients and to compare the results with those in the literature.

Of all the patients included in the current analysis, 79.5% showed at least one lesion with characteristics suggestive of recurrent PCa on  $^{68}\text{Ga}$ -PSMA-11 PET/CT performed 1 h after injection. This rate is slightly lower than we have found previously [21]. The lower PSA values (median PSA 2.2 in this study vs. 4.6 in our previous study) is probably the main reason for the lower detection rates in this study. However, the detection rates in this study are still remarkably different from the 89.5% found by Eiber et al. [22]. As the imaging protocol and amounts of injected activity are similar, the reasons for this discrepancy remain speculative. Patient selection might be one reason.

**Fig. 1** Probabilities of a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan (a) and plot of the rates of pathological PET/CT scans with confidence intervals (b) in relation to PSA levels in 971 patients. *Blue columns* Numbers of patients with a pathological PET/CT scan together with the rates which also represent the patient-based sensitivities of  $^{68}\text{Ga}$ -PSMA-11 PET/CT in detecting recurrent PCa in relation to PSA level. Amongst all patients with a PSA level less than 0.2 ng/ml, 15 had values less than 0.1 ng/ml

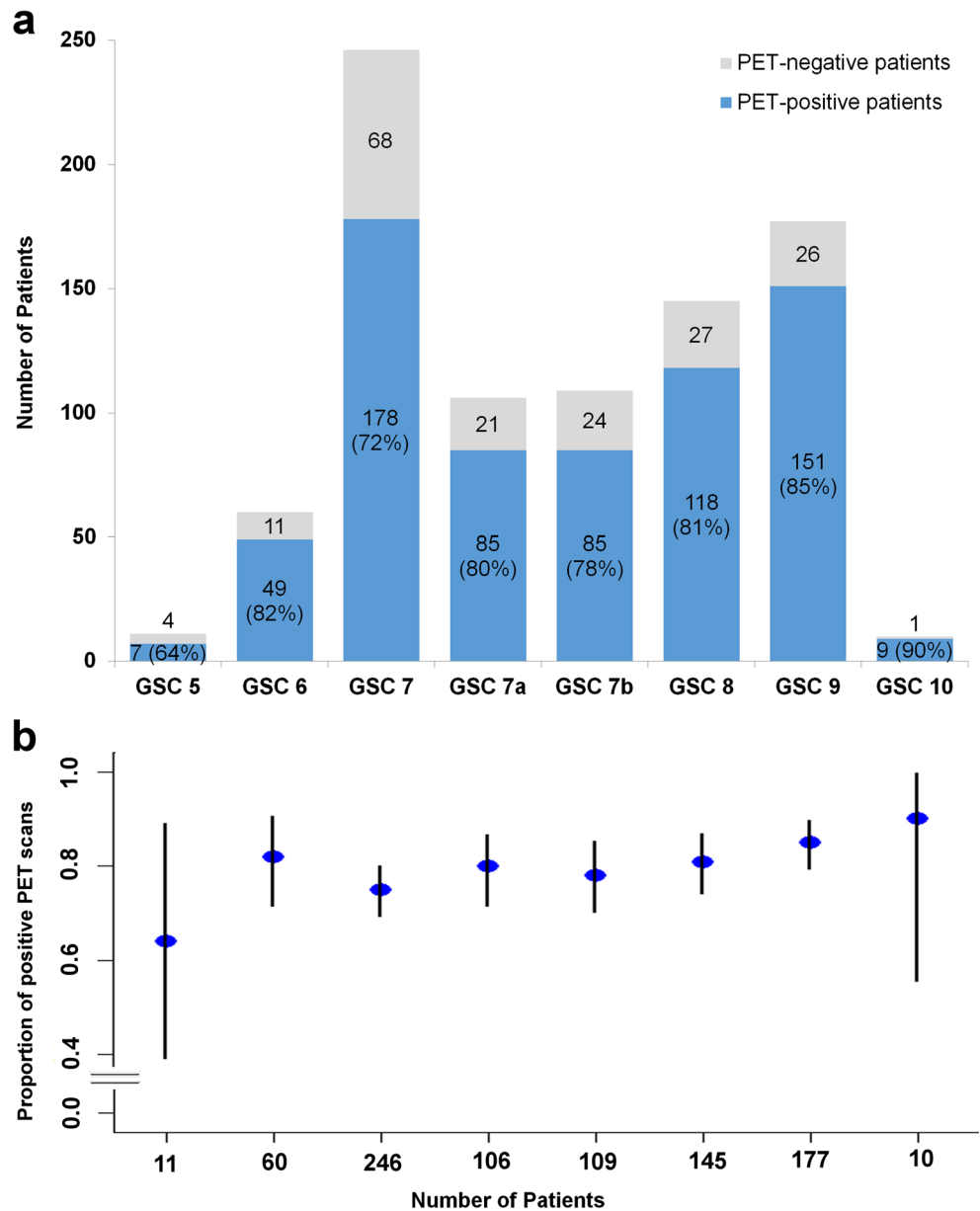


Recently, several studies have shown that tumour-to-background ratios (contrast) and tumour uptake of various PSMA ligands increase in the majority of PCa lesions with time [19, 28–35]. Comparison of different PSMA ligands therefore strictly requires scans to be performed within the same time frame after injection. One of the studies mentioned demonstrated that the higher uptake and contrast of PCa lesions in scans obtained 3 h after injection result in a higher number of lesions detected by  $^{68}\text{Ga}$ -PSMA-11 PET/CT as well as in a higher number of patients with a pathological PET result [35]. In a small cohort of patients analysed for dosimetry, the optimal imaging time for  $^{68}\text{Ga}$ -PSMA-11 seemed to be at 3 h after injection [31]. However,  $^{68}\text{Ga}$ -PSMA-11 PET/CT is routinely performed 1 h after injection

in accordance with the clinical set-up first described [19]. Therefore, this novel method of imaging could easily be integrated into clinical routine as a range of other PET scans with different tracers (e.g. FDG, DOTA conjugates etc.) are also routinely performed at 1 h after injection. However, as described above, additional late scans with  $^{68}\text{Ga}$ -PSMA-11 can help clarify unclear findings or increase the probability of tumour detection in patients with a negative early scan [35].

It can be assumed that all patients included in this analysis had recurrent disease and that our cohort did not include true-negative cases. Therefore, calculating patient-based specificity, and negative and positive predictive values was not possible. However, with regard to a patient-based analysis, it is apparent that  $^{68}\text{Ga}$ -PSMA-11 is able to detect PCa with good sensitivity.

**Fig. 2** Probabilities of a pathological <sup>68</sup>Ga-PSMA-11 PET/CT scan (a) and plot of the rates of pathological PET/CT scans with confidence intervals (b) in relation to GSC in 864 patients. The GSC 7 bar includes those patients in whom the subclassification (7a or 7b) was unknown. Blue columns Numbers of patients with a pathological PET/CT scan together with the rates



**Table 2** Multivariate logistic regression analysis of the associations between different variables and a pathological <sup>68</sup>Ga-PSMA-11 PET/CT scan including only the variables that were available in all 755 patients, with Gleason score as a continuous variable

Variable	Coefficient	Standard error	p value	Odds ratio	95% confidence interval
Constant	0.963	0.961	0.316	2.618	0.398–17.206
Age <sup>a</sup>	-0.0125	0.131	0.924	0.988	0.764–1.276
Injected activity <sup>b</sup>	0.00245	0.0715	0.973	1.002	0.871–1.153
Androgen deprivation therapy	0.592	0.275	0.032	1.807	1.053–3.100
Log PSA	0.735	0.0776	<0.001	2.086	1.792–2.429
Gleason score $\geq 7b$	0.0964	0.241	0.689	1.101	0.686–1.767

<sup>a</sup> Analysed as multiples of 10 years

<sup>b</sup> Analysed as multiples of 50 MBq

**Table 3** Multivariate logistic regression analysis of the associations between different variables and a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan including only the variables that were available in all 755 patients, with Gleason score as a categorical variable

Variable	Coefficient	Standard error	<i>p</i> value	Odds ratio	95% confidence interval
Constant	0.796	0.994	0.423	2.217	0.316–15.548
Age <sup>a</sup>	−0.0239	0.132	0.856	0.976	0.754–1.265
Injected activity <sup>b</sup>	0.0136	0.0716	0.849	1.014	0.881–1.166
Androgen deprivation therapy	0.528	0.279	0.058	1.696	0.982–2.929
Log PSA	0.747	0.0790	<0.001	2.110	1.808–2.464
Gleason score					
7	0.201	0.363	0.580	1.222	0.600–2.489
8	0.231	0.421	0.584	1.260	0.551–2.878
9 + 10	0.711	0.421	0.092	2.035	0.891–4.648

<sup>a</sup> Analysed as multiples of 10 years

<sup>b</sup> Analysed as multiples of 50 MBq

The multivariate analysis demonstrated a strong association between a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan and PSA level. This result confirms previously reported results and was expected as an increase in PSA levels usually indicates progressive disease in differentiated PCa. However, as demonstrated in Fig. 1, a continuous increase in PSA level does not always correlate with an increase in tumour detection. Not all patients, even those with a PSA level above 10 ng/ml, had a pathological scan (Fig. 1). Although according to the literature almost all prostatic adenocarcinomas express PSMA [36, 37], the level of PSMA expression can be regarded as decisive for a pathological PSMA ligand scan. Other reasons for a negative scan despite PSA elevation could be dedifferentiation of the tumour, tumour size below the spatial resolution of the PET scanner, the stage of technology of the PET scanner, and tumours adjacent to the urinary bladder. Recent studies have demonstrated a higher sensitivity of late  $^{68}\text{Ga}$ -PSMA-11 PET/CT including oral hydration and administration of a diuretic [35, 38].

One of the most important questions in PSMA-imaging concerns the role of ADT. It is known from preclinical studies

that ADT can increase PSMA expression in PCa cells [39, 40]. The finding of this preclinical observation in the clinical setting could have a significant impact on both imaging and therapy with PSMA ligands. Recently, Hope et al. demonstrated that ADT is able to increase PSMA expression in PCa metastases and to increase the number of lesions visualized by PSMA PET. This effect, which has been observed before in cell and animal models, has been seen in one patient [41]. Confirming the results of our previous study [21], the current analysis demonstrated that patients receiving ADT at the time of  $^{68}\text{Ga}$ -PSMA-11 PET/CT more frequently presented with a positive scan than patients without ADT at the time of the scan. However, this result needs to be interpreted with caution as patients with advanced disease could be more likely to receive ADT. On the other hand, ADT usually causes reductions in tumour volumes and PSA values. Both of these effects have a negative impact on tumour detection on imaging. In contrast to our findings, Eiber et al. could not find a significant association between an ADT (within the last 6 months prior to the scan) and the probability of a pathological  $^{68}\text{Ga}$ -PSMA-11

**Table 4** Multivariate logistic regression analysis of the associations between different variables and a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan in 260 patients in whom  $\text{PSA}_{\text{DT}}$  data were available, with  $\text{PSA}_{\text{DT}}$  as a continuous variable

Variable	Coefficient	Standard error	<i>p</i> value	Odds ratio	95% confidence interval
Constant	0.960	1.752	0.584	2.611	0.0843–80.893
Age <sup>a</sup>	0.0429	0.236	0.856	1.044	0.657–1.658
Injected activity <sup>b</sup>	−0.0454	0.121	0.708	0.956	0.754–1.211
Androgen deprivation therapy	0.273	0.446	0.540	1.314	0.549–3.149
Log PSA	0.644	0.138	<0.001	1.904	1.452–2.497
Gleason score $\geq 7$ <sup>b</sup>	−0.220	0.450	0.625	0.802	0.332–1.938
$\text{PSA}_{\text{DT}}$	0.000253	0.000391	0.518	1.000	0.999–1.001

<sup>a</sup> Analysed as multiples of 10 years

<sup>b</sup> Analysed as multiples of 50 MBq

**Table 5** Multivariate logistic regression analysis of the associations between different variables and a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan in 260 patients in whom  $\text{PSA}_{\text{DT}}$  data were available, with  $\text{PSA}_{\text{DT}}$  as a categorical variable

Variable	Coefficient	Standard error	<i>p</i> value	Odds ratio	95% confidence interval
Constant	1.008	2.039	0.621	2.741	0.0503–149.230
Age <sup>a</sup>	0.0348	0.241	0.885	1.035	0.645–1.661
Injected activity <sup>b</sup>	−0.0551	0.122	0.651	0.946	0.745–1.201
Androgen deprivation therapy	0.191	0.450	0.672	1.210	0.501–2.925
Log PSA	0.644	0.139	<0.001	1.904	1.450–2.499
Gleason score $\geq 7$ <sup>b</sup>	−0.298	0.456	0.514	0.742	0.303–1.816
$\text{PSA}_{\text{DT}}$ (days)					
31–90	0.705	0.913	0.440	2.024	0.338–12.122
91–180	0.0667	0.881	0.940	1.069	0.190–6.008
181–365	−0.136	0.879	0.877	0.873	0.156–4.887
>365	0.453	0.917	0.621	1.573	0.261–9.489

<sup>a</sup> Analysed as multiples of 10 years

<sup>b</sup> Analysed as multiples of 50 MBq

PET/CT scan [22]. Different analyzing methods and including criteria might be reasons for this discrepancy.

In accordance with our results published previously, there was only a tendency for an association without significance between higher GSC and a higher probability of a pathological PET/CT scan. The detection rate among patients with GSC 6 was slightly higher than among those with GSC 7/8. As mentioned above, no clear relationship between GSC and the PET result was found in the main analysis. Thus, any differences in detection rate between GSC classes were most likely the result of chance. Indeed, the confidence intervals for GSC 6 and GSC 7/8 (Fig. 2) strongly overlapped. Therefore, no real differences between the GSC groups can be concluded. In contrast to other analyses, we were able to analyse GSC 7a and 7b separately, but did not observe any relevant differences between the groups. A positive correlation between higher GSC and

PSMA expression has been demonstrated in preclinical studies [42–44]. In contrast to our group, Eiber et al. found a significantly positive association between higher GSC and a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan in 221 patients. In accordance with the results of previous studies including more than 200 patients [21, 22], no association was found between a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan and patient age or  $\text{PSA}_{\text{DT}}$ . This result was expected as we do not assume any correlation between proliferation index and PSMA expression of the tumours. However, studies with smaller patient cohorts have shown a significant role of  $\text{PSA}_{\text{DT}}$  [25, 26].

The multivariate analysis also did not show any association between  $\text{PSA}_{\text{Vel}}$  and a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan. Our explanation for this observation is the same as for  $\text{PSA}_{\text{DT}}$ . Also no association was found between the amount of injected activity and a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT

**Table 6** Multivariate logistic regression analysis of the associations between different variables and a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan in 61 patients in whom  $\text{PSA}_{\text{DT}}$  and  $\text{PSA}_{\text{Vel}}$  data were also available, with  $\text{PSA}_{\text{DT}}$  and  $\text{PSA}_{\text{Vel}}$  as continuous variables

Variable	Coefficient	Standard error	<i>p</i> value	Odds ratio	95% confidence interval
Constant	0.686	3.732	0.854	1.986	0.00132–2.982.909
Age <sup>a</sup>	0.159	0.521	0.760	1.173	0.423–3.253
Injected activity <sup>b</sup>	−0.177	0.282	0.531	0.838	0.482–1.457
Androgen deprivation therapy	0.137	0.894	0.878	1.147	0.199–6.617
lnPSA	0.822	0.280	0.003	2.276	1.315–3.940
GSC $\geq 7$ <sup>b</sup>	−0.623	0.966	0.519	0.536	0.0808–3.563
$\text{PSA}_{\text{DT}}$	0.000882	0.00145	0.544	1.001	0.998–1.004
$\text{PSA}_{\text{Vel}}$	−0.0105	0.00702	0.135	0.990	0.976–1.003

<sup>a</sup> Analysed as multiples of 10 years

<sup>b</sup> Analysed as multiples of 50 MBq



scan. In our previous study including 319 patients a noticeable but nonsignificant positive association was also observed between a positive  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan and lower amounts of injected activity [21]. We assumed that statistical variability was the sole explanation for this unexpected finding. The results of the current study confirm this assumption.

In order to provide an individualized calculation of the probability of a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan at 1 h after injection, a Microsoft Excel file was created and is attached to the supplementary data of this article (Supplementary File 1). By inserting individual patient parameter values (age, ADT, PSA level and GSC), the probability of a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan can be calculated. However, it has to be emphasized that the values calculated are only approximate, and no warranty can be given for the calculated ratios and percentages.

One limitation of this study is the lack of an analysis of histological patterns in patients who were treated by surgery after  $^{68}\text{Ga}$ -PSMA-11 PET/CT. The main reason is that the majority of the patients were not treated at our centre. Biopsies and operative findings not obtained at our hospital were not included in this evaluation due to insufficient access to the pathological reports. In addition, the histology data would have to be interpreted with great caution because no standardized approach was followed. For instance, results stratified by individual lymph nodes may be strongly biased by the inclusion of individual patients with large numbers of lymph nodes removed or patients with exclusive removal of individual suspicious lymph nodes. Furthermore, probably only those patients with clear-cut PET findings and/or findings of other conventional imaging modalities underwent surgery. On the other hand, the high specificity of  $^{68}\text{Ga}$ -PSMA-11 for the detection of PCa has been histologically well documented in several studies [21, 22, 34, 45–49]. Although uptake of PSMA ligands in various nonprostate tissues has been reported [50–61], it has to be emphasized that the number of nonprostate lesions detected represents only a fraction of the overwhelming numbers of PCa lesions detected daily by PSMA ligand imaging worldwide. According to the experience so far, any uptake of  $^{68}\text{Ga}$ -PSMA-11 (and possibly also of alternative PSMA ligands currently clinically used) above local background in lesions morphologically visible on CT or MRI is highly specific for PCa. However, this statement is currently valid only in patients with a rising PSA level after initial treatment of PCa.

## Conclusion

$^{68}\text{Ga}$ -PSMA-11 PET/CT can detect recurrent PCa in a high percentage of patients with recurrent PCa. The probability of a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan is strongly associated with PSA level and ongoing ADT. Only a tendency for an association without significance was found between higher GSC and a higher probability of a pathological PET/CT scan.

No association was found between a pathological  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan and patient age, amount of injected activity,  $\text{PSA}_{\text{DT}}$  or  $\text{PSA}_{\text{Vel}}$ .

**Acknowledgments** A huge number of people helped to plan this study, and investigate and analyse the patients in the past years. Amongst them are (in alphabetical order): H. Adam, S. Biedenstein, R. Brück, E. Dahlke, L. Engel, T. Gerwert, Prof. B. Hadaschik, D. Johna, Dr. C. Kleist, Dr. S. Krämer, K. Kunze, V. Reischwich, F. Seybold-Epting, P. Seybold-Epting, and N. Zimmermann.

## Compliance with ethical standards

**Ethical approval** All patients included in this study signed written informed consent form for anonymized evaluation and publication of their data. All reported investigations were conducted in accordance with the principles of the Declaration of Helsinki and with our national regulations (German Medicinal Products Act, AMG §13 2b). This study was approved by the ethics committee of the University of Heidelberg (S-321-2012).

**Conflicts of interest** None.

## References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2014;64:9–29.
2. Israeli RS, Powell CT, Corr JG, Fair WR, Heston WD. Expression of the prostate-specific membrane antigen. *Cancer Res.* 1994;54:1807–11.
3. Wright GL Jr, Grob BM, Haley C, Grossman K, Newhall K, Petylak D, et al. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. *Urology.* 1996;48:326–34.
4. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. *Urology.* 1998;52:637–40.
5. Chang SS. Overview of prostate-specific membrane antigen. *Rev Urol.* 2004;6 Suppl 10:S13–8.
6. Jochumsen MR, Vendelbo MH, Høyer S, Bouchelouche K. Subcutaneous lobular capillary hemangioma on  $^{68}\text{Ga}$ -PSMA PET/CT. *Clin Nucl Med.* 2017;42(4):e214–5.
7. Noto B, Weckesser M, Buerke B, Pixberg M, Avramovic N. Gastrointestinal stromal tumor showing intense tracer uptake on PSMA PET/CT. *Clin Nucl Med.* 2017;42(3):200–2.
8. Dias AH, Holm Vendelbo M, Bouchelouche K. Prostate-specific membrane antigen PET/CT: uptake in lymph nodes with active sarcoidosis. *Clin Nucl Med.* 2017;42(3):e175–6.
9. Zacho HD, Nielsen JB, Dettmann K, Haberkorn U, Petersen LJ. Incidental detection of thyroid metastases from renal cell carcinoma using  $^{68}\text{Ga}$ -PSMA PET/CT to assess prostate cancer recurrence. *Clin Nucl Med.* 2017;42(3):221–2.
10. Damle NA, Tripathi M, Chakraborty PS, Sahoo MK, Bal C, Aggarwal S, et al. Unusual uptake of prostate specific tracer ( $^{68}\text{Ga}$ -PSMA-HBED-CC) in a benign thyroid nodule. *Nucl Med Mol Imaging.* 2016;50:344–7.
11. Stephens M, Kim DI, Shepherd B, Gustafson S, Thomas P. Intense uptake in amyloidosis of the seminal vesicles on  $^{68}\text{Ga}$ -PSMA PET mimicking locally advanced prostate cancer. *Clin Nucl Med.* 2017;42:147–8.
12. Sasikumar A, Joy A, Nanabala R, Pillai MR, Hari TA.  $^{68}\text{Ga}$ -PSMA PET/CT false-positive tracer uptake in Paget disease. *Clin Nucl Med.* 2016;41:e454–5.

13. Bilgin R, Ergül N, Çermik TF. Incidental meningioma mimicking metastasis of prostate adenocarcinoma in 68Ga-labeled PSMA ligand PET/CT. *Clin Nucl Med*. 2016;41:956–8.
14. Vamadevan S, Le K, Bui C, Mansberg R. Prostate-specific membrane antigen uptake in small cleaved B-cell follicular non-Hodgkin lymphoma. *Clin Nucl Med*. 2016;41:980–1.
15. Bhardwaj H, Stephens M, Bhatt M, Thomas PA. Prostate-specific membrane antigen PET/CT findings for hepatic hemangioma. *Clin Nucl Med*. 2016;41:968–9.
16. Vamadevan S, Shetty D, Le K, Bui C, Mansberg R, Loh H. Prostate-specific membrane antigen (PSMA) avid pancreatic neuroendocrine tumor. *Clin Nucl Med*. 2016;41:804–6.
17. Kanthan GL, Iazard MA, Emmett L, Hsiao E, Schembri GP. Schwannoma showing avid uptake on 68Ga-PSMA-HBED-CC PET/CT. *Clin Nucl Med*. 2016;41:703–4.
18. Noto B, Vrachimis A, Schäfers M, Stegger L, Rahbar K. Subacute stroke mimicking cerebral metastasis in 68Ga-PSMA-HBED-CC PET/CT. *Clin Nucl Med*. 2016;41:e449–51.
19. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. *Eur J Nucl Med Mol Imaging*. 2013;40:486–95.
20. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2014;41:11–20.
21. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:197–209.
22. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2015;56:668–74.
23. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, et al. Prospective comparison of 18F-fluoromethylcholine versus 68Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. *J Nucl Med*. 2015;56:1185–90.
24. Schwenck J, Rempp H, Reischl G, Kruck S, Stenzl A, Nikolaou K, et al. Comparison of (68)Ga-labelled PSMA-11 and (11)C-choline in the detection of prostate cancer metastases by PET/CT. *Eur J Nucl Med Mol Imaging*. 2017;44:92–101.
25. Ceci F, Uprimny C, Nilica B, Geraldo L, Kendler D, Kroiss A, et al. (68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging*. 2015;42:1284–94.
26. Verburg FA, Pfister D, Heidenreich A, Vogg A, Drude NI, Vöö S, et al. Extent of disease in recurrent prostate cancer determined by [(68)Ga]PSMA-HBED-CC PET/CT in relation to PSA levels, PSA doubling time and Gleason score. *Eur J Nucl Med Mol Imaging*. 2016;43:397–403.
27. Eder M, Neels O, Müller M, Bauder-Wüst U, Remde Y, Schäfer M, et al. Novel preclinical and radiopharmaceutical aspects of [68Ga]Ga-PSMA-HBED-CC: a new PET tracer for imaging of prostate cancer. *Pharmaceuticals (Basel)*. 2014;7:779–96.
28. Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, et al. Radiation dosimetry and first therapy results with a (124)I/(131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. *Eur J Nucl Med Mol Imaging*. 2014;41:1280–92.
29. Herrmann K, Bluemel C, Weineisen M, Schottelius M, Wester H-J, Czernin J, et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. *J Nucl Med*. 2015;56:855–61.
30. Afshar-Oromieh A, Hetzheim H, Kratochwil C, Benesova M, Eder M, Neels OC, et al. The theranostic PSMA ligand PSMA-617 in the diagnosis of prostate cancer by PET/CT: biodistribution in humans, radiation dosimetry, and first evaluation of tumor lesions. *J Nucl Med*. 2015;56:1697–705.
31. Afshar-Oromieh A, Hetzheim H, Kübler W, Kratochwil C, Giesel FL, Hope TA, et al. Radiation dosimetry of (68)Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. *Eur J Nucl Med Mol Imaging*. 2016;43:1611–20.
32. Pfoh CH, Ziegler S, Graner FP, Köhner M, Schachoff S, Blechert B, et al. Biodistribution and radiation dosimetry of (68)Ga-PSMA HBED CC – a PSMA specific probe for PET imaging of prostate cancer. *Eur J Nucl Med Mol Imaging*. 2016;43:1962–70.
33. Szabo Z, Mena E, Rowe SP, Plyku D, Nidal R, Eisenberger MA, et al. Initial evaluation of [(18)F]JDCFPyL for prostate-specific membrane antigen (PSMA)-targeted PET imaging of prostate cancer. *Mol Imaging Biol*. 2015;17:565–74.
34. Sahlmann C-O, Meller B, Bouter C, Ritter CO, Ströbel P, Lotz J, et al. Biphaseic 68Ga-PSMA-HBED-CC-PET/CT in patients with recurrent and high-risk prostate carcinoma. *Eur J Nucl Med Mol Imaging*. 2016;43:898–905.
35. Afshar-Oromieh A, Sattler LP, Mier W, Hadaschik B, Debus J, Holland-Letz T, et al. The clinical impact of additional late PET/CT imaging with 68Ga-PSMA-11 (HBED-CC) in the diagnosis of prostate cancer. *J Nucl Med*. 2017. doi:10.2967/jnumed.116.183483
36. Ross JS, Sheehan CE, Fisher HAG, Kaufman RP, Kaur P, Gray K, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res*. 2003;9:6357–62.
37. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res*. 1997;3:81–5.
38. Derlin T, Weiberg D, von Klot C, Wester H-J, Henkenberens C, Ross TL, et al. (68)Ga-PSMA I&T PET/CT for assessment of prostate cancer: evaluation of image quality after forced diuresis and delayed imaging. *Eur Radiol*. 2016;26:4345–53.
39. Evans MJ, Smith-Jones PM, Wongvipat J, Navarro V, Kim S, Bander NH, et al. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. *Proc Natl Acad Sci U S A*. 2011;108:9578–82.
40. Liu T, Wu LY, Fulton MD, Johnson JM, Berkman CE. Prolonged androgen deprivation leads to downregulation of androgen receptor and prostate-specific membrane antigen in prostate cancer cells. *Int J Oncol*. 2012;41:2087–92.
41. Hope TA, Truillet CC, Ehman EC, Afshar-Oromieh A, Aggarwal R, Ryan CJ, et al. Imaging response to androgen receptor inhibition using 68Ga-PSMA-11 PET: first human experience. *J Nucl Med*. 2017;58(1):81–4.
42. Marchal C, Redondo M, Padilla M, Caballero J, Rodrigo I, García J, et al. Expression of prostate specific membrane antigen (PSMA) in prostatic adenocarcinoma and prostatic intraepithelial neoplasia. *Histol Histopathol*. 2004;19:715–8.
43. Kasperzyk JL, Finn SP, Flavin R, Fiorentino M, Lis R, Hendrickson WK, et al. Prostate-specific membrane antigen protein expression in tumor tissue and risk of lethal prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2013;22:2354–63.
44. Minner S, Wittmer C, Graefen M, Salomon G, Steuber T, Haese A, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. *Prostate*. 2011;71:281–8.
45. Herlemann A, Wenter V, Kretschmer A, Thierfelder KM, Bartenstein P, Faber C, et al. (68)Ga-PSMA positron emission

- tomography/computed tomography provides accurate staging of lymph node regions prior to lymph node dissection in patients with prostate cancer. *Eur Urol.* 2016;70:553–7.
46. Maurer T, Weirich G, Schottelius M, Weineisen M, Frisch B, Okur A, et al. Prostate-specific membrane antigen-radioguided surgery for metastatic lymph nodes in prostate cancer. *Eur Urol.* 2015;68:530–4.
  47. Pfister D, Porres D, Heidenreich A, Heidegger I, Knuechel R, Steib F, et al. Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with (68)Ga-PSMA-HBED-CC than with (18)F-fluoroethylcholine PET/CT. *Eur J Nucl Med Mol Imaging.* 2016;43:1410–7.
  48. Hijazi S, Meller B, Leitsmann C, Strauss A, Meller J, Ritter CO, et al. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by 68Ga-PSMA-positron emission tomography/computerized tomography. *Prostate.* 2015;75:1934–40.
  49. Rowe SP, Gage KL, Faraj SF, Macura KJ, Cornish TC, Gonzalez-Roibon N, et al. 18F-DCFBC PET/CT for PSMA-based detection and characterization of primary prostate cancer. *J Nucl Med.* 2015;56:1003–10.
  50. Artigas C, Alexiou J, Garcia C, Wimana Z, Otte F-X, Gil T, et al. Paget bone disease demonstrated on (68)Ga-PSMA ligand PET/CT. *Eur J Nucl Med Mol Imaging.* 2016;43:195–6.
  51. Rischpler C, Maurer T, Schwaiger M, Eiber M. Intense PSMA-expression using (68)Ga-PSMA PET/CT in a paravertebral schwannoma mimicking prostate cancer metastasis. *Eur J Nucl Med Mol Imaging.* 2016;43:193–4.
  52. Schwenck J, Tabatabai G, Skardelly M, Reischl G, Beschoner R, Pichler B, et al. In vivo visualization of prostate-specific membrane antigen in glioblastoma. *Eur J Nucl Med Mol Imaging.* 2015;42:170–1.
  53. Sathekge M, Lengana T, Modiselle M, Vorster M, Zeevaart J, Maes A, et al. (68)Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients. *Eur J Nucl Med Mol Imaging.* 2017;44(4):689–94.
  54. Sasikumar A, Joy A, Nanabala R, Pillai MRA, Thomas B, Vikraman KR. (68)Ga-PSMA PET/CT imaging in primary hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging.* 2016;43:795–6.
  55. Verburg FA, Krohn T, Heinzl A, Mottaghy FM, Behrendt FF. First evidence of PSMA expression in differentiated thyroid cancer using [68Ga]PSMA-HBED-CC PET/CT. *Eur J Nucl Med Mol Imaging.* 2015;42:1622–3.
  56. Sawicki LM, Buchbender C, Boos J, Giessing M, Ermert J, Antke C, et al. Diagnostic potential of PET/CT using a (68)Ga-labelled prostate-specific membrane antigen ligand in whole-body staging of renal cell carcinoma: initial experience. *Eur J Nucl Med Mol Imaging.* 2017;44:102–7.
  57. Demirci E, Ocak M, Kabasakal L, Decristoforo C, Talat Z, Halaç M, et al. (68)Ga-PSMA PET/CT imaging of metastatic clear cell renal cell carcinoma. *Eur J Nucl Med Mol Imaging.* 2014;41:1461–2.
  58. Rhee H, Blazak J, Tham CM, Ng KL, Shepherd B, Lawson M, et al. Pilot study: use of gallium-68 PSMA PET for detection of metastatic lesions in patients with renal tumour. *EJNMMI Res.* 2016;6:76.
  59. Lütje S, Sauerwein W, Lauenstein T, Bockisch A, Poeppel TD. In vivo visualization of prostate-specific membrane antigen in adenoid cystic carcinoma of the salivary gland. *Clin Nucl Med.* 2016;41:476–7.
  60. Rowe SP, Gorin MA, Hammers HJ, Som Javadi M, Hawasli H, Szabo Z, et al. Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted 18F-DCFpYl PET/CT. *Ann Nucl Med.* 2015;29:877–82.
  61. Rowe SP, Gorin MA, Hammers HJ, Pomper MG, Allaf ME, Javadi MS. Detection of 18F-FDG PET/CT occult lesions with 18F-DCFpYl PET/CT in a patient with metastatic renal cell carcinoma. *Clin Nucl Med.* 2016;41:83–5.