

# The Role of PSMA PET Imaging in Prostate Cancer Theranostics: A Nationwide Survey

Angelika Borkowetz<sup>a</sup> Johannes Linxweiler<sup>b</sup> Sebastian Fussek<sup>c</sup>  
Bernd Wullich<sup>d</sup> Matthias Saar<sup>e</sup> on behalf of the German Prostate Cancer Consortium (DPKK)

<sup>a</sup>Department of Urology, University Hospital, Technische Universität Dresden, Dresden, Germany; <sup>b</sup>Department of Urology, Saarland University, Homburg, Germany; <sup>c</sup>Urologische Praxis Pappelallee, Greifswald, Germany; <sup>d</sup>Department of Urology and Paediatric Urology, University Hospital, Erlangen, Germany; <sup>e</sup>Department of Urology, University Hospital, Aachen, Germany

## Keywords

PSMA PET imaging · Prostate cancer · Radioligand therapy · Theranostics · Survey · Biochemical recurrence · Metastatic castration-resistant prostate cancer

## Abstract

**Introduction:** Prostate-specific membrane antigen (PSMA)-based imaging and theranostics have played an important role in the diagnosis, staging, and treatment of prostate cancer (PCa). We aimed to evaluate the acceptance and use of PSMA theranostics among German urologists. **Methods:** An anonymous online questionnaire was sent via survio.com to the members of the German Society of Urology (DGU). **Results:** Seventy-two percent of participants performed PSMA positron emission tomography (PET) imaging regularly in biochemically recurrent PCa. Overall, 61% of participants considered PSMA-radioligand therapy to be very useful or extremely useful. PSMA PET imaging in high-risk PCa is more often considered by urologists working in a university setting than in nonuniversity settings or medical practices (51% vs. 25%,  $p < 0.001$ ). Most perform PSMA-radioligand therapy as an option after all approved systemic treatments for met-

astatic castration-resistant PCa (56%) or after cabazitaxel (14%). A total of 93.9% and 70.3% of respondents consider the lack of reimbursement by health insurance to be the main obstacle to using PSMA PET imaging or radioligand therapy, respectively. **Discussion/Conclusion:** PSMA-based imaging/theranostics are already widely applied but would find even more widespread use if reimbursement is clearly regulated by health insurance in Germany.

© 2022 The Author(s).

Published by S. Karger AG, Basel

## Introduction

In the last decade, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging and PSMA-targeted therapy (PSMA theranostics) have played an important role in the diagnostic workup of newly diagnosed high-risk prostate cancer (PCa) or in the setting of biochemical recurrence after local treatment as

Angelika Borkowetz and Johannes Linxweiler contributed equally to this work.

**Table 1.** Characteristics of survey participants

Parameter	
Age, years, median (IQR)	52 (43–59)
Gender, <i>n</i> (%)	
Male	280 (85)
Female	48 (15)
Certified urologists, <i>n</i> (%)	316 (96)
Certified physicians, <i>n</i> (%)	
Urologists	325 (99)
Radiologists	1 (0.3)
Radiooncologists	1 (0.3)
Nuclear medicine	–
Regions, <i>n</i> (%)	
West Germany	65 (20)
East Germany	263 (80)
Area, <i>n</i> (%)	
Rural-suburban (<20,000 citizens)	49 (15)
Urban (20,000–100,000 citizens)	95 (29)
Metropolitan (>100,000 citizens)	184 (56)
Practice type, <i>n</i> (%)	
University hospital	55 (17)
Academic hospital	22 (7)
Communal hospital	58 (17)
Medical practice	193 (59)
Duration of work, <i>n</i> (%)	
1–5 years	14 (4)
6–10 years	37 (11)
11–20 years	88 (27)
>20 years	189 (58)
Number of patients with PCa/quarter, <i>n</i> (%)	
<50	54 (17)
50–100	114 (35)
101–200	103 (31)
201–500	57 (17)
>500	–
Number of patients with mCRPC/quarter, <i>n</i> (%)	
<10	52 (16)
11–20	108 (33)
21–50	125 (38)
51–100	35 (11)
>100	8 (2.4)

well as in the treatment of advanced metastatic castration-resistant PCa (mCRPC). PSMA PET computed tomography (CT) or magnetic resonance imaging (MRI) demonstrates higher sensitivity and higher specificity in the detection of metastases in high-risk PCa [1] and at biochemical recurrence after local therapy compared to conventional staging imaging by abdominal CT and bone scintigraphy [2, 3]. Moreover, PSMA-radioligand therapy shows greater effectiveness with respect to PSA responses [4] and imaging-based progression-free survival as well as overall survival [5] compared to cabazitaxel and standard-of-care treatment in mCRPC. However, the

benefit of PSMA PET imaging in the primary diagnosis and staging of PCa is still unclear [6, 7]. Recently, published data indicate that the use of PSMA PET imaging might enhance the visualization and detection rate of PCa [8]. Therefore, the PRIMARY trial investigating the detection of clinically significant PCa by a combination of PSMA PET-CT with multiparametric MRI compared to targeted biopsies and the probability of avoiding unnecessary prostate biopsies will provide conclusions in the future [9].

International and national guidelines recommend PSMA PET imaging for staging in high-risk PCa and in cases of biochemical recurrence after local treatment [10–12]. PSMA-radioligand therapy is recommended as the last-line treatment in mCRPC patients [12] or is still regarded as investigational [10, 11]. However, data from the recently published TheraP and VISION trials [5] will be suitable to change the current recommendations for PSMA-radioligand therapy.

Despite the promising results of PSMA PET imaging and PSMA-targeted therapy in the diagnosis and treatment of PCa, reimbursement and access to facilities offering PSMA theranostics are still limiting factors in Germany. The aim of this study was to evaluate the acceptance and use of PSMA theranostics among German urologists in clinical and medical practice settings. Moreover, potential reasons for obstacles to access to PSMA theranostics are investigated.

## Material and Methods

### Survey

A 30-item questionnaire was designed to collect demographic data and information on German urologists' opinions regarding the use of PSMA PET imaging in primary diagnosis, staging in newly diagnosed PCa, biochemical recurrence, and metastatic disease. Moreover, further questions aimed to explore the use of PSMA-directed radioligand therapy in mCRPC. The questionnaire contained open questions, multiple choice questions, and certain questions that allowed respondents to "select all that apply." Information was obtained on the respondents' age, gender, practice region, urban area, practice type, level of training, years in practice, number of treated patients with (metastatic) PCa, and use of PSMA PET in daily practice. Furthermore, the circumstances and obstacles regarding the use of PSMA imaging and theranostics were explored.

### Study Design

A link to the survey together with a personal invitation from the German Prostate Cancer Consortium (DPKK) was sent twice with a time interval of 6 weeks through email to all members of the German Society of Urology (DGU). With over 6,500 members, this society is one of the largest medical societies in Germany, with a

**Table 2.** Participants' answers to questions on the use of PSMA PET imaging

	n (%)
What imaging do you regularly perform on patients with high-risk prostate cancer prior to initial therapy? (multiple answers possible)	
CT abdomen/pelvis	274 (83.5)
Bone scan	290 (88.4)
MRI abdomen/pelvis or whole-body MRI	101 (30.8)
FDG PET-CT/MRI	1 (0.3)
Choline PET-CT/MRI	0
PSMA PET-CT/MRI	96 (29.3)
PSMA scan	4 (1.2)
What imaging do you regularly perform on patients with biochemical recurrence after local therapy of prostate cancer? (multiple answers possible)	
CT abdomen/pelvis	182 (55.5)
Bone scan	189 (57.6)
MRI abdomen/pelvis or whole-body MRI	85 (25.9)
FDG PET-CT/MRI	3 (0.9)
Choline PET-CT/MRI	8 (2.4)
PSMA PET-CT/MRI	240 (73.2)
PSMA scan	9 (2.7)
What imaging do you regularly perform on patients with metastatic prostate cancer under systemic treatment? (multiple answers possible)	
CT abdomen/pelvis	274 (83.5)
Bone scan	276 (84.1)
MRI abdomen/pelvis or whole-body MRI	60 (18.3)
FDG PET-CT/MRI	1 (0.3)
Choline PET-CT/MRI	2 (0.6)
PSMA PET-CT/MRI	116 (35.4)
PSMA scan	2 (0.6)
Would you send a patient with suspected prostate cancer for PSMA PET-CT/MRI before histological confirmation?	
Yes	32 (9.8)
No	296 (90.2)
In which patients do you consider a PSMA PET-CT/MRI useful? (multiple answers)	
For primary diagnostic in patients with prior negative prostate biopsy and rising PSA	56 (17.1)
In patients with high-risk PCa before local treatment	177 (54)
In patients with persistent PSA after radical prostatectomy	271 (82.6)
In patients with biochemical recurrence after radical prostatectomy	315 (96)
In patients with biochemical recurrence after percutaneous radiotherapy/brachytherapy	274 (83.5)
In patients with progressive metastatic prostate cancer under systemic treatment	179 (54.6)
At what PSA level do you initiate PSMA PET-CT/MRI diagnostics if the patient shows biochemical recurrence after radical prostatectomy?	
<0.2 ng/mL	4 (1.2)
0.2–0.5 ng/mL	157 (47.9)
0.5–1 ng/mL	126 (38.4)
>1 ng/mL	41 (12.5)
Do you have unlimited access to PSMA PET imaging?	
Yes	143 (43.6)
No	185 (56.4)
If no, what are the difficulties that prevent you from ordering PSMA PET imaging? (multiple answers possible)	(197 respondents)
Too far for the patients to travel	30 (15.2)
Completely missing nuclear medicine infrastructure	20 (6.1)
Lack of reimbursement of costs by health insurances	185 (93.9)
Missing recommendations by the guidelines or consensus paper	14 (23.4)
Examination not useful	2 (1)

**Table 2** (continued)

	n (%)
What do you see as the advantage of PSMA PET-CT/MRI diagnostics and a possible therapeutic use? (multiple answers possible)	
More precise staging compared to abdominal CT and bone scan	260 (79.3)
Exclusion of metastases	198 (60.4)
Metastasis-directed local therapy	269 (82)
Before PSMA-radioligand therapy	217 (66.2)
Do you submit cost coverage requests for PSMA PET-CT/MRI diagnostics for your patients with public health insurance?	
Yes	122 (37.2)
No	92 (28)
Is performed by the nuclear medicine	114 (34.8)
How often is the cost of PSMA PET imaging covered by health insurance?	
Never	29 (8.8)
Very rare	81 (24.7)
Sometimes	127 (38.7)
Regularly	72 (22)
Always	19 (5.8)

heterogeneous member population of clinicians and urologic practitioners in communal and academic hospitals or in ambulant offices. Approximately, 5,087 members received the email invitation. The responses were collected in an SPSS spreadsheet in an anonymous fashion. Statistical analyses were performed using SPSS version 26.0 (IBM, Mount Kisco, NY, USA). Univariate logistic regression analyses were performed to identify factors associated with the use of PSMA PET imaging in the mentioned indications: primary diagnosis and tumour staging for recurrent PCa after local treatment and for metastatic stage ("Which imaging technique do you perform regularly in high-risk PCa, in recurrent PCa, or the metastatic stage under systemic treatment?"). Respondents' age, gender, practice region, urban area, practice type, level of training, experience in urology practice, and experience in treating PCa patients were used in regression analyses. For significant associations identified in the univariate regression analyses, all factors were identified that changed the calculated odds ratio (OR) >10% and these were included in the respective multivariate model. Statistical significance was defined as  $p < 0.05$ .

## Results

### PSMA PET Imaging

A total of 328 responses (response rate 328/5,087; 6%) were received. The characteristics of the participants are detailed in Table 1. The mean age of the participants was 50.7 years ( $\pm 11$ ), 85.4% were male, and 14.6% were female. A total of 96.3% were trained urologists, with an overall distribution in favour of those practising in a medical practice (58.8%). Tables 2 and 3

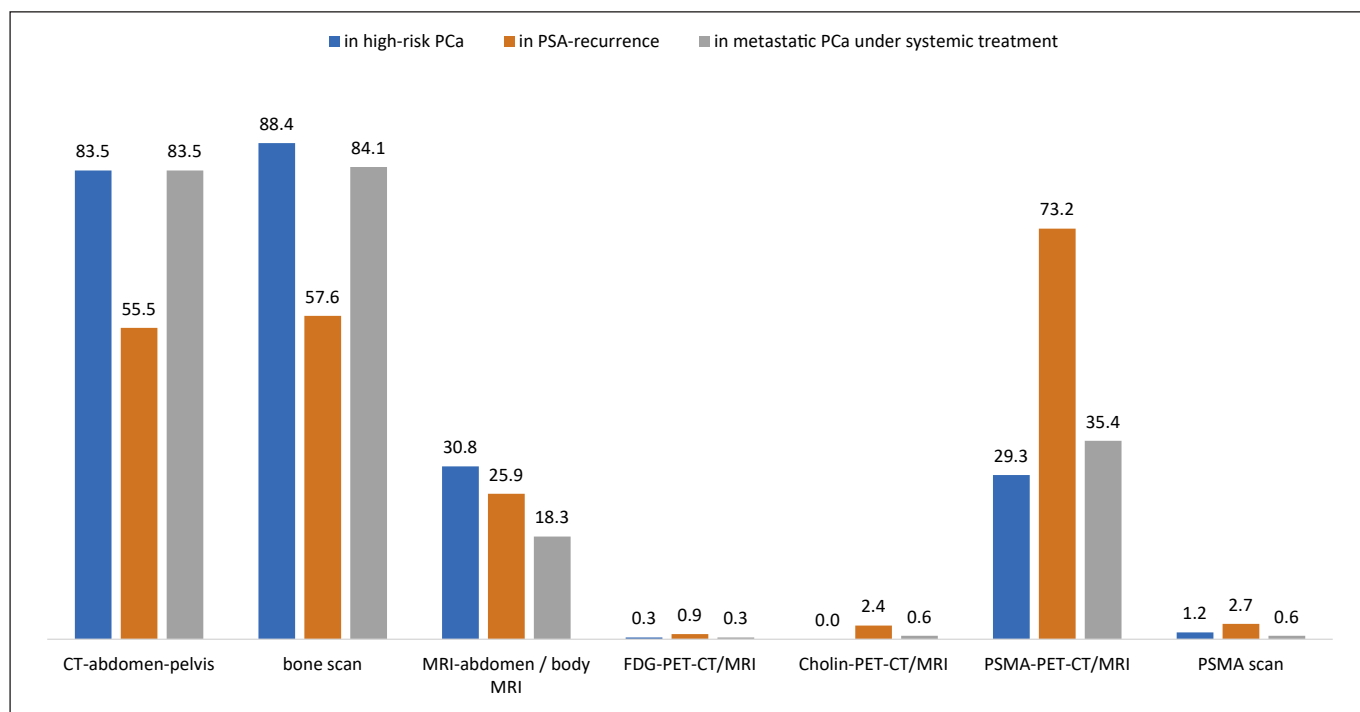
give an overview of the participants' answers to all survey questions.

Seventy-two percent of participants performed PSMA PET imaging regularly in biochemically recurrent PCa after local treatment. Abdominal CT and bone scans dominate the primary staging of high-risk PCa and metastatic disease under systemic treatment (PSMA PET imaging 29.3% and 35.5%, respectively) (Fig. 1). PSMA PET imaging in high-risk PCa is more often considered by urologists working in a university setting than in nonuniversity settings or a medical practice (51% vs. 25%,  $p < 0.001$ ). PSMA PET imaging in PSA recurrence is also more often used in a university setting (87% vs. 70%,  $p = 0.01$ ). However, independent predictors for the use of PSMA PET imaging in high-risk PCa are access to the facilities (OR 3.5 [95% CI: 2–6];  $p < 0.001$ ), the location in a metropolitan region (OR 2.2 [95%-CI: 1.3–3.6];  $p = 0.003$ ), and reimbursement by health insurance (OR 1.7 [95% CI: 1–2.1];  $p = 0.045$ ) in the case of biochemical recurrence (Table 4). In the case of biochemical recurrence, 47.9% and 38.4% of respondents would use PSMA PET at PSA levels of 0.2–0.5 ng/mL and 0.5–1 ng/mL, respectively. Only 1.2% would consider this method at a PSA level <0.2 ng/mL, and another 12.5% would use PSMA PET imaging at PSA levels >1 ng/mL. Most respondents (90%) did not use PSMA PET imaging for primary diagnosis.

The respondents considered PSMA PET imaging useful in the staging of high-risk PCa, PSA persistence after

**Table 3.** Participants' answers to questions on the use of PSMA-radioligand therapy

	n (%)
Do you have access to a centre that offers PSMA-ligand therapy?	
Yes	282 (86)
No	46 (14)
If no, what are the difficulties that prevent them from being able to offer PSMA-radioligand therapy to their patients? (multiple answers possible)	(64 respondents)
Too far for the patients to travel	25 (39.1)
Completely missing nuclear medicine infrastructure	17 (26.6)
I do not perform systemic treatment	4 (6.3)
Lack of reimbursement of costs by health insurances	45 (70.3)
How useful do you consider PSMA-ligand therapy for the treatment of metastatic castration-resistant prostate cancer (mCRPC)?	
Extremely useful	40 (12.2)
Very useful	161 (49.1)
Moderately useful	114 (34.8)
Hardly useful	13 (4)
Not at all useful	0
After how many prior therapies for mCRPC would you be most likely to use PSMA-ligand therapy for the first time?	
One	11 (3.4)
Two	55 (16.8)
Three	67 (20.4)
Four	13 (4)
After all approved or available therapies	182 (55.5)
Is there a patient group to whom you would particularly recommend PSMA-ligand therapy due to their metastatic pattern? (multiple answers possible)	
Only lymphatic metastasis	31 (9.5)
Osseous and lymphatic metastasis	118 (36)
Pure osseous metastasis	45 (13.7)
Visceral metastasis	61 (18.6)
Therapy is offered regardless of the metastasis pattern	146 (44.5)
Do not send patients to this therapy	25 (7.6)
At what point in the sequential therapy of mCRPC do you foresee the use of PSMA-ligand therapy?	
Early use of ligand therapy in the second/third line when bone marrow reserve is still sufficient	70 (21.3)
Ligand therapy only after use of Cabazitaxel	30 (9.1)
Use of ligand therapy before use of Cabazitaxel	44 (13.4)
Use only after all therapeutic options have been exhausted	184 (56.1)
In your experience, how tolerable is PSMA-ligand therapy?	
Extremely tolerable	3 (0.9)
Very tolerable	118 (36)
Moderately tolerable	196 (59.8)
Hardly tolerable	196 (59.8)
Not at all tolerable	8 (2.4)
How often do you see serious adverse events ( $\geq$ CTCAE grade 3) after PSMA-ligand therapy?	
Extremely rare	30 (9.2)
Very rarely	108 (32.9)
Occasionally	163 (49.7)
Frequently	24 (7.3)
Always	2 (0.6)
Would you advise the patient against PSMA-ligand therapy because of the side effects?	
Yes	11 (3.4)
No	317 (96.6)



**Fig. 1.** Use of imaging modalities in high-risk PCa, in biochemical recurrence after local treatment, and in mCRPC under systemic treatment.

radical prostatectomy, biochemical recurrent disease, and the metastatic stage under systemic treatment, with proportions of 54%, 82.6%, 96%, and 54.6%, respectively (Fig. 2). The advantages of PSMA PET imaging and as a potentially therapeutic approach are evident for metastasis-directed therapy (82%), more precise staging compared to abdominal CT and bone scans (79.3%), exclusion of metastases before local treatment (60.4%) and before PSMA-radioligand therapy (66.2%).

A total of 43.6% of respondents reported difficulties obtaining PSMA PET imaging for their patients. A total of 197 participants (60%) responded to the question regarding obstacles to obtaining PSMA PET imaging, with 93.9% of these respondents considering the lack of reimbursement by health insurance to be an obstacle to using PSMA PET imaging in diagnostics. No differences for reimbursement were identified among urologists working in a clinic or in medical practices. Moreover, only 28% of all participants reported that health insurance covered the costs regularly (22%) or always (6%).

#### *PSMA-Radioligand Therapy*

Most respondents (86%) had access to PSMA-radioligand therapy independent from the workplace. Addi-

tionally, the lack of reimbursement is the main obstacle to referring patients to this treatment (70.3%). However, only 61% of participants considered PSMA-radioligand therapy to be very useful or extremely useful. Most consider PSMA-radioligand therapy to be an option after all approved systemic treatments for mCRPC (56%) or after cabazitaxel (14%). Only 21% would implement this treatment option earlier during the second or third line of treatment. PSMA-radioligand therapy is regarded as a treatment option independent of the metastatic pattern (44.5%) or mainly in lymphatic and bone metastases (36%). Most of the respondents considered PSMA-radioligand therapy to be moderately to extremely tolerable and would not recommend against this treatment due to side effects (97%).

#### **Discussion**

The first and most relevant indication for PSMA PET/CT is probably biochemical recurrence after local curative therapy, such as radical prostatectomy [13]. Here, PSMA PET/CT allows the detection of the location of tumour recurrence in many cases, enabling metastasis-di-

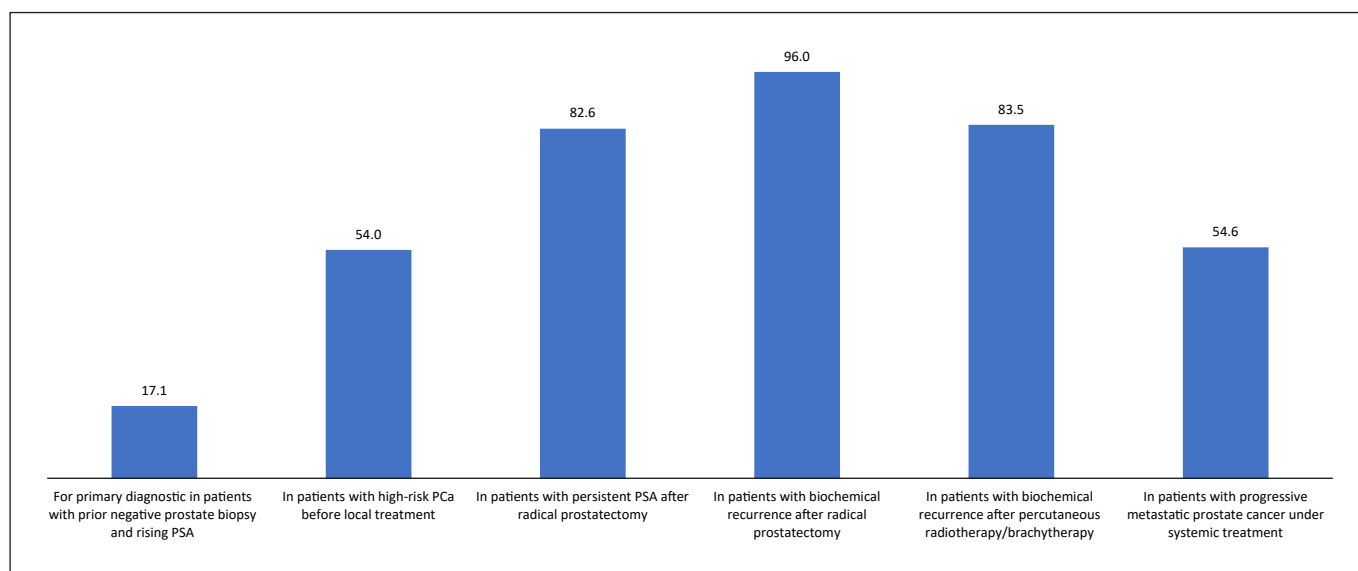


**Table 4.** Logistic regression analysis

	In high-risk PCa before local treatment		In biochemical recurrence after local treatment		mCRPC		In primary diagnostic after prior negative biopsy	
	univariate, OR (95% CI; p value)	multivariate, OR (95% CI; p value)	univariate, OR (95% CI; p value)	multivariate, OR (95% CI; p value)	univariate, OR (95% CI; p value)	multivariate, OR (95% CI; p value)	univariate, OR (95% CI; p value)	multivariate, OR (95% CI; p value)
Age ≤ vs. >median (50a)	-	-	-	-	-	-	-	-
University/academic hospital vs. communal hospital/medical practice	2.4 (1.4–4.1; 0.001)	2.1 (1.2–9; 0.016)	-	-	-	-	-	-
Medical practice vs. university/academic/communal hospital	-	-	0.5 (0.3–0.8; 0.005)	0.8 (0.5–1.2; 0.263)	-	-	-	-
Certified urologist yes vs. no	-	-	-	-	-	-	-	-
Duration of practice ≤10 vs. >10a	-	-	-	-	-	-	-	-
East vs. West Germany	-	-	-	-	-	-	-	-
Metropolitan vs. nonmetropolitan	2.5 (1.5–4.1; <0.001)	1.9 (1.1–3.2; 0.26)	1.7 (1.03–2.7; 0.037)	2.2 (1.3–3.6; 0.003)	-	-	-	-
Number of treated PCa patients/quarter >100 vs. ≤100	2.1 (1.3–2.4; 0.003)	1.7 (0.9–3.2; 0.106)	-	-	1.8 (1.2–2.9; 0.009)	-	-	-
Number of treated mCRPC patients >20 vs. ≤20	2.5 (1.5–4.0; <0.001)	1.8 (0.9–3.3; 0.076)	-	-	-	-	-	-
Access vs. no access to PSMA PET imaging facilities	4.1 (2.5–6.9; <0.001)	3.5 (2–6; <0.001)	-	-	-	-	-	-
Reimbursement often vs. not often	1.9 (1.2–3.2; 0.012)	0.9 (0.5–1.7; 0.806)	5.3 (2.4–11.5; <0.001)	1.7 (1–2.1; 0.045)	-	-	0.16 (0.36–0.663; 0.012)	-

rected therapy in terms of salvage lymph node dissection or targeted radiotherapy [14–16]. Our survey is in line with this finding and shows that most of the participants would use PSMA PET imaging in the setting of biochemical recurrence and at a PSA level between 0.2 and 0.5 ng/mL. In several studies, the probability of positive PSMA PET/CT at biochemical recurrence has been clearly demonstrated to increase with higher PSA values and a shorter PSA doubling time [17–19]. Of note, PSMA PET/CT seems to be equally useful in the diagnostic workup and treatment planning in patients with PSA recurrence after curative-intent EBRT [20, 21]. However, in Germany, reimbursement for PSMA PET/CT for this indication is still a huge issue, especially outside academic centres, hampering its widespread use. Although PSMA PET/CT is clearly recommended for patients with biochemical recurrence in the German and European guidelines when the results of this examination have therapeutic implications, 93.3% of the participants in our survey reported problems with reimbursement by health insurance as the main obstacle to using PSMA PET/CT for diagnostic purposes. A long travelling distance to the site of imaging acquisition, a lack of nuclear medicine infrastructure or missing recommendations for PSMA PET/CT by medical societies seem to be less relevant reasons not to perform this kind of imaging (15.2%, 6.2%, and 23.5%, respectively). Only 43.6% had unlimited access to PSMA PET imaging. However, since 2021, so-called outpatient specialist care (ASV) agreements have offered the opportunity to reimburse PSMA PET imaging in the outpatient setting. However, these ASV centres are not established at all hospital outpatient departments and individual practices.

An increasingly discussed indication for PSMA PET/CT is the staging of high-risk PCa. Here, the proPSMA trial provided high-level evidence that PSMA PET/CT is superior to conventional imaging concerning diagnostic accuracy, with a sensitivity of 85% (PSMA PET/CT) versus 38% (conventional imaging) and a specificity of 98% (PSMA PET/CT) versus 91% (conventional imaging) for the detection of metastases [1]. Of note, an analysis in the proPSMA trial demonstrated that the use of PSMA PET/CT instead of conventional imaging is cost-effective in patients with high-risk PCa [22]. Based on these data, PSMA PET imaging is recommended in the German S3 guidelines [12]. However, the EAU guidelines mention PSMA PET imaging but do not recommend its use and refer to possible treatment changes due to the more sensitive detection of metastasis [11]. However, only 29.3% of our participants would use PSMA PET/CT for primary staging in high-risk PCa, with significantly more urologists



**Fig. 2.** Participants' opinions on the usefulness of PSMA PET imaging for different indications.

working in a university setting than in nonuniversity settings or medical practices considering PSMA PET/CT in such patients.

In contrast to primary staging, most of our participants regarded PSMA PET/CT as useful before PSMA-radioligand therapy in patients with mCRPC, which is consistent with current evidence-based recommendations, with most departments of nuclear medicine performing PSMA and FDG PET/CT before PSMA-radioligand therapy to ensure the expression of the therapeutic target and exclude the presence of so-called mismatch metastases (PSMA negative and FDG positive) [23, 24]. Moreover, PSMA PET/CT-derived metabolic parameters seem to be associated with treatment results [25].

In line with the increasingly frequent use of PSMA PET imaging in cases of tumour progression in mCRPC, the use of targeted ligand therapy against the surface molecule PSMA is a consecutive treatment sequence. However, in our survey, only 61% of respondents regarded PSMA-radioligand therapy as extremely useful. Most of the respondents use PSMA-radioligand therapy according to the current German S3 guidelines in a late line in cases of tumour progression in mCRPC [12]. The German S3 guideline recommends PSMA-radioligand therapy after exhausting all therapeutic options as a grade 3 level of evidence [12]. In contrast, the EAU guidelines present PSMA-radioligand therapy only in a background context [10, 11].

PSMA-radioligand therapy is applied as a 4- to 6-cycle treatment with an applied activity of 6–7.4 GBq each cycle. One-third of treated patients have responded to the treatment, and a further one-third has shown at least stable disease [26, 27]. Moreover, the main side effects (such as mouth dryness and haematopoietic toxicity) occurring during treatment are not a reason to advise against the treatment by the surveyed urologists. Most of them regarded this treatment as very to moderately tolerable. Serious side effects are regarded as very rare or occasional.

The updated German S3 guideline was published in April 2021. Shortly after the updating process, the data of the Australian TheraP trial were published. In this prospective phase II trial, PSMA-radioligand therapy showed an important benefit in the PSA response compared to cabazitaxel in patients with progressing mCRPC after docetaxel therapy and primary PSMA enrichment in metastatic sites [4]. Additionally, the subsequently published VISION trial supported the results of the TheraP trial. Moreover, this phase III trial demonstrated significantly longer overall survival with PSMA-radioligand therapy than with the standard of care [5]. Both trials were published during the survey, and if the survey had been conducted later, the rate of those who recommended PSMA-radioligand therapy may be assumed to have been quite higher.

In particular, since access to PSMA-radioligand therapy is quite high (86% of respondents), the request for this



therapy could be expandable. Again, the lack of reimbursement is the main obstacle to referring patients to this treatment (71% of respondents). Until now, in Germany, treatment with PSMA-radioligand therapy has been reimbursed by public health insurance after individual application of cost coverage by the insured, which might change soon, as the FDA and EMA are currently reviewing the use of PSMA-radioligand therapy based on data from the latest trials.

### Limitations

This study has a number of limitations. In addition to the basic problems of a survey, such as responses in terms of social desirability, a low response rate of approximately 6% might be the strongest limitation. However, a total sample of 328 respondents with a well-balanced distribution between public hospitals and private practices seems to reflect the urological community appropriately. In addition, a strong selection bias exists due to the linking of the survey in the digital newsletter of the professional society. Moreover, most participants were urologists since the survey was conducted via the DGU. Next, only the German point of view was evaluated in this survey. Despite these methodological limitations, our survey provides a valuable picture of the use of PSMA theranostics within the DGU. The evaluation of the use of PSMA PET imaging and radioligand therapy among European and international systems is pending. Therefore, a survey of European therapists might give an indication of the use of this imaging and therapy modality on an international level.

### Conclusion

This survey evaluated the acceptance and use of PSMA theranostics among German urologists. PSMA PET imaging is mainly performed in biochemical recurrent PCa. For staging in high-risk PCa, PSMA PET is mainly used by urologists working in an academic setting. While PSMA PET imaging is favoured, especially in high-risk PCa and in cases of PCa recurrence, PSMA-radioligand therapy is mainly considered in late stages of mCRPC. Unfortunately, the lack of reimbursement is still the main obstacle to transferring patients to PSMA-based imaging or treatment. We conclude that PSMA PET imaging and radioligand therapy would find even more widespread use if reimbursement is clearly regulated by health insurance in Germany.

### Acknowledgment

We thank Olaf Kurpick for preparation of the questionnaire and for support with the technical details.

### Statement of Ethics

This study was performed according to the Helsinki Declaration. Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent from participants was not required in accordance with local/national guidelines.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

### Author Contributions

Angelika Borkowetz: study concept, data collection, data analysis, data interpretation, drafting of the manuscript, and revision of the manuscript. Johannes Linxweiler: study concept, data interpretation, drafting of the manuscript, and revision of the manuscript. Sebastian Fussek and Matthias Saar: study concept. Bernd Wullich: conception and design, supervision, and revision of the manuscript.

### Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

### References

- 1 Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet*. 2020;395(10231):1208–16.
- 2 Caroli P, Sandler I, Matteucci F, De Giorgi U, Uccelli L, Celli M, et al. (68)Ga-PSMA PET/CT in patients with recurrent prostate cancer after radical treatment: prospective results in 314 patients. *Eur J Nucl Med Mol Imaging*. 2018;45(12):2035–44.

- 3 Afshar-Oromieh A, Holland-Letz T, Giesel FL, Kratochwil C, Mier W, Haufe S, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging*. 2017; 44(8):1258–68.
- 4 Hofman MS, Emmett L, Sandhu S, Irvani A, Joshua AM, Goh JC, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*. 2021;397(10276):797–804.
- 5 Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385(12):1091–103.
- 6 Sonni I, Felker ER, Lenis AT, Sisk AE, Bahri S, Allen-Auerbach MS, et al. Head-to-head comparison of (68)Ga-PSMA-11 PET/CT and mpMRI with histopathology gold-standard in the detection, intra-prostatic localization and local extension of primary prostate cancer: results from a prospective single-center imaging trial. *J Nucl Med*. 2021;63(6):847–54.
- 7 Baggeley D, Ong S, Buteau JP, Koschel S, Dhi-antravan N, Hofman MS, et al. Role of PSMA PET/CT imaging in the diagnosis, staging and restaging of prostate cancer. *Future Oncol*. 2021;17(17):2225–41.
- 8 Celen S, Gultekin A, Ozlulderden Y, Mete A, Sagtas E, Ufuk F, et al. Comparison of 68Ga-PSMA-I/T PET-CT and multiparametric MRI for locoregional staging of prostate cancer patients: A Pilot Study. *Urol Int*. 2020; 104(9–10):684–91.
- 9 Amin A, Blazeviski A, Thompson J, Scheltema MJ, Hofman MS, Murphy D, et al. Protocol for the PRIMARY clinical trial, a prospective, multicentre, cross-sectional study of the additive diagnostic value of gallium-68 prostate-specific membrane antigen positron-emission tomography/computed tomography to multiparametric magnetic resonance imaging in the diagnostic setting for men being investigated for prostate cancer. *BJU Int*. 2020; 125(4):515–24.
- 10 Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2021; 79(2):243–62.
- 11 Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. part II-2020 update: treatment of relapsing and metastatic prostate cancer. *Eur Urol*. 2021;79(2): 263–82.
- 12 Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. S3-Leitlinie Prostatakarzinom Version 6.2. 2021.
- 13 Kopp D, Kopp J, Bernhardt E, Manka L, Beck A, Gerullis H, et al. 68Ga-Prostate-Specific membrane antigen positron emission tomography-computed tomography-based primary staging and histological correlation after extended pelvic lymph node dissection in intermediate-risk prostate cancer. *Urol Int*. 2022; 106(1):56–62.
- 14 Rogowski P, Trapp C, von Bestenbostel R, Eze C, Ganswindt U, Li M, et al. Outcome after PSMA-PET/CT-based salvage radiotherapy for nodal recurrence after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2022; 49(4):1417–28.
- 15 Linxweiler J, Sprenk J, Cascetta K, Prylukhin A, Holters S, Zeuschner P, et al. Robotic salvage lymph node dissection in recurrent prostate cancer: lessons learned from 68 cases and implications for future clinical management. *J Urol*. 2021;206(1):88–96.
- 16 Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or metastasis-directed therapy for oligo-metastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36(5):446–53.
- 17 Verburg FA, Pfister D, Heidenreich A, Vogg A, Drude NJ, Voo 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(3):397–403.
- 18 Cerci JJ, Fanti S, Lobato EE, Kunikowska J, Alonso O, Medina S, et al. Diagnostic performance and clinical impact of (68)Ga-PSMA-11 PET/CT imaging in early relapsed prostate cancer after radical therapy: a prospective multicenter study (IAEA-PSMA Study). *J Nucl Med*. 2022;63(2):240–7.
- 19 Hoffmann MA, Buchholz HG, Wieler HJ, Miederer M, Rosar F, Fischer N, et al. PSA and PSA kinetics thresholds for the presence of (68)Ga-PSMA-11 PET/CT-detectable lesions in patients with biochemical recurrent prostate cancer. *Cancers*. 2020;12(2):E398.
- 20 Pfister D, Haidl F, Nestler T, Verburg F, Schmidt M, Wittersheim M, et al. (68)Ga-PSMA-PET/CT helps to select patients for salvage radical prostatectomy with local recurrence after primary radiotherapy for prostate cancer. *BJU Int*. 2020;126(6):679–83.
- 21 Farolfi A, Calderoni L, Mattana F, Mei R, Telo S, Fanti S, et al. Current and emerging clinical applications of PSMA PET diagnostic imaging for prostate cancer. *J Nucl Med*. 2021; 62(5):596–604.
- 22 de Faria Cardet RE, Hofman MS, Segard T, Yim J, Williams S, Francis RJ, et al. Is prostate-specific membrane antigen positron emission tomography/computed tomography imaging cost-effective in prostate cancer: an analysis informed by the proPSMA trial. *Eur Urol*. 2021;79(3):413–8.
- 23 Khreish F, Ribbat K, Bartholoma M, Maus S, Stemler T, Hierlmeier I, et al. Value of combined PET imaging with [(18)F]FDG and [(68)Ga]Ga-PSMA-11 in mCRPC patients with worsening disease during [(177)Lu]Lu-PSMA-617 RL. *Cancers*. 2021;13(16):4134.
- 24 Michalski K, Ruf J, Goetz C, Seitz AK, Buck AK, Lapa C, et al. Prognostic implications of dual tracer PET/CT: PSMA ligand and [(18)F]FDG PET/CT in patients undergoing [(177)Lu]PSMA radioligand therapy. *Eur J Nucl Med Mol Imaging*. 2021;48(6):2024–30.
- 25 Schmidkonz C, Cordes M, Schmidt D, Bauerle T, Goetz TI, Beck M, et al. (68)Ga-PSMA-11 PET/CT-derived metabolic parameters for determination of whole-body tumor burden and treatment response in prostate cancer. *Eur J Nucl Med Mol Imaging*. 2018; 45(11):1862–72.
- 26 Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schafers M, Essler M, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med*. 2017; 58(1):85–90.
- 27 Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol*. 2018; 19(6):825–33.