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^{68}Ga-PSMA-11 PET/CT: the rising star of nuclear medicine in prostate cancer imaging?

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Summary Ever since the introduction of ^{68}Ga-prostate-specific membrane antigen 11 positron-emission tomography/computed tomography (^{68}Ga-PSMA-11 PET/CT) a few years ago, it has rapidly achieved great success in the field of prostate cancer imaging. A large number of studies have been published to date, indicating a high potential of ^{68}Ga-PSMA-11 PET/CT in the work-up of prostate cancer patients, including primary diagnosis, staging and biochemical recurrence. The aim of this review is to present the most important data on this novel, highly promising imaging technique, and to formulate recommendations for possible applications of ^{68}Ga-PSMA-11 PET/CT in clinical routine.

Keywords ^{68}Ga-PSMA-11 PET/CT · Prostate cancer · Indication · Staging · Biochemical recurrence

Introduction

Prostate cancer (PC) constitutes the most frequent solid tumour among men in Western countries [1, 2]. Prognosis of PC patients is correlated with the tumour stage and the aggressiveness of the tumour, expressed histopathologically with Gleason scores [3]; survival probability is significantly lower in patients in whom metastases are diagnosed. The most common sites of PC metastases are lymph nodes (LN) and bone, followed by liver and lung in advanced stages [4, 5]. Accurate assessment of local and distant metastases is of crucial importance for optimal therapeutic decision making. Besides exact tumour localisation, imaging modalities should deliver precise and reliable information on the extent of newly diagnosed and relapsing PC [3, 6]. These requirements are only partially met by currently applied imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), which are mainly based on morphological criteria, but also bone scintigraphy has serious limitations [7, 8].

The introduction of dedicated PET/CT scanners combining morphological and molecular information almost 20 years ago is considered to represent a milestone in the diagnostic work-up of different tumour entities. In general, as a whole-body imaging technique, PET/CT enables screening for local and distant metastases in one single examination. Regarding PET imaging of PC, ^{11}C- and ^{18}F-labelled choline agents have been widely used over many years [9, 10]. However, initially very promising data on choline-based tracers could not be confirmed during the course of time. A major drawback of choline tracers is the fact that increased uptake of choline, which is integrated in cell membrane synthesis, is also found in various other tissues and diseases not related to PC. In fact, in clinical application, choline PET/CT has been proven to exhibit limited sensitivity, especially with respect to assessment of LN [11–17].

In the 1990s, prostate-specific membrane antigen (PSMA) was identified as a cell membrane bound protein showing an overexpression in prostatic cells [18, 19]. Although prostate epithelial cells and benign high-grade prostatic intraepithelial neoplasia also exhibit increased PSMA expression, PSMA is upregulated many-fold in adenocarcinoma of the prostate and its metastases [20]. In case of PC, PSMA expression seems to be associated with tumour differentiation. In immunohistochemical studies, PC with Gleason primary patterns 4 and 5 displayed a higher extent of PSMA staining than lower grades of PC [20]. Despite its name, PSMA expression is not exclusively

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restricted to prostatic tissue, as extraprostatic PSMA expression is also found in duodenal mucosa, renal tubules, salivary glands, colonic cells and, interestingly, in the endothelium of neovascular capillaries in several epithelial malignancies [18, 21–23]. Nevertheless, given the significantly higher PSMA expression in nearly all PC compared to normal prostate tissue [19], it has been realised that PSMA could represent an ideal cell molecule for PC imaging with radiopharmaceuticals targeting PSMA. Amongst different approaches, the ^{68}Ga-labelled PSMA ligand Glu-NH-CO-NH-Lys(Ahx)-HBED-CC was successfully introduced for PET/CT imaging of PC in 2012 [24–28]. Glu-NH-CO-NH-Lys(Ahx)-HBED-CC, also referred to as ^{68}Ga-PSMA-11, is an inhibitor of PSMA that binds with high affinity to the external domain of PSMA, and is internalised thereafter and trapped within the cell [26, 27, 29]. As it does not exert any physiologic or pathologic effect on the cell, this tracer fulfils the requirements for application in humans. Initial clinical experiences suggested that this novel tracer is superior to ^{18}F-choline [30], showing a rapid clearance from the blood pool with a good contrast between tumour lesions and most normal tissues 60 min after tracer injection, when image acquisition is usually performed [25]. Two subsequent studies could demonstrate high detection rates of ^{68}Ga-PSMA-11-positive lesions consistent with metastases in PC patients with biochemical recurrence, even at very low PSA values [30, 31]. Furthermore, ^{68}Ga-PSMA-11 can easily be produced on site, which makes it accessible to most institutions with PET/CT facilities [26–28]. Although there is markedly increased tracer uptake in the urinary tract, small bowel, liver, spleen, salivary glands and lacrimal gland, physiologically, ^{68}Ga-PSMA-11 shows a very low uptake at locations that are mostly affected by metastases, such as the iliac and retroperitoneal region as well as bone [25, 32]. Due to these favourable characteristics, the application of ^{68}Ga-PSMA-11 PET/CT for imaging PC has been constantly increasing during the past few years, prompting an avalanche of published literature concerning ^{68}Ga-PSMA-11-PET/CT and PC imaging. In addition to rapidly growing data on the use of ^{68}Ga-PSMA-11 PET/CT, PET/MRI scanners were recently introduced into clinical practice, with encouraging preliminary results in PC imaging using ^{68}Ga-PSMA-11 as a PET tracer [33, 34]. As this novel device is currently restricted to only few centres worldwide, the present review will only partly deal with the issue, focusing mainly on the application and potential indications of ^{68}Ga-PSMA-11 PET/CT.

Diagnosis and detection of prostate cancer

In patients with suspicion of PC based on persistently elevated prostate-specific antigen (PSA) values or digital rectal examination, systematic transrectal ultrasound (TRUS)-guided biopsy is recommended as the first diagnostic approach to prove PC [4]. Multiparametric MRI (mpMRI) has been proven to establish a sensitive method for detecting PC and should be applied after negative systematic TRUS biopsies [4, 35, 36].

With respect to PET imaging, sufficient tumour-related tracer accumulation exceeding the uptake of surrounding tissue constitutes a prerequisite for tumour detection. The majority of PC seems to show an increased tracer uptake on ^{68}Ga-PSMA-11 PET, as also indicated in a clinical trial by Maurer et al. [37]. In 130 patients assessed for primary staging, they could demonstrate that 91.6% of primary tumours exhibited a higher tracer uptake than normal prostate tissue. The intensity of ^{68}Ga-PSMA-11 accumulation in the primary tumour seems to correlate with Gleason score (GS), with higher GS showing a more intense tracer uptake compared to lower GS [38]. However, regarding ^{68}Ga-PSMA-11 and diagnosis of PC, to date, only limited data on ^{68}Ga-PSMA-11 are available. In a prospective study, Eiber et al. performed simultaneous ^{68}Ga-PSMA-11 PET/MRI in 53 histologically verified PC patients, with histopathologic evaluation after radical prostatectomy serving as a standard of reference [39]. In addition to a higher specificity of ^{68}Ga-PSMA-11 PET compared to mpMRI (94 vs. 82%) they could find a significantly higher detection rate of PC with PET and PET/MRI compared to mpMRI alone, with patient-based sensitivities of 92, 98 and 66%, respectively. In a comparative trial including 20 patients with localised PC scheduled for prostatectomy, Rhee et al. could demonstrate that additional performance of ^{68}Ga-PSMA-11 PET enhances the diagnostic accuracy of mpMRI, mainly due to excellent specificity of ^{68}Ga-PSMA-11 [40]. However, the study also showed that a significant number of cancers were missed by both imaging modalities. As to detection of tumour lesions in the prostate gland, a region-based analysis, with postoperative whole-mount histopathology serving as a reference, yielded a sensitivity and specificity of 44 and 94% for mpMRI compared to 49 and 95% for ^{68}Ga-PSMA-11 PET/CT, respectively. The authors state that tumour detectability is associated with tumour size, as cancer lesions not identified by both modalities demonstrated a median size of 8 mm, in comparison to a median size of 22.5 mm of tumours visible on mpMRI and ^{68}Ga-PSMA-11 PET/CT. Given the risk of missing smaller tumour lesions, they concluded that both mpMRI and ^{68}Ga-PSMA-11 PET/CT cannot reliably substitute standardized TRUS-guided biopsy and ^{68}Ga-PSMA-11 PET/CT should only be used in addition to mpMRI in this setting. Nevertheless, at least from a clinical point of view, performance of ^{68}Ga-PSMA-11 PET/CT seems to be justified in patients with repeatedly negative TRUS biopsies, in order to guide biopsies to PET-positive areas.

However, the potential role of ^{68}Ga-PSMA-11 PET/CT in primary diagnosis needs to be elucidated in larger, preferably prospective trials. At present, due

to lack of data, performance of ^{68}Ga-PSMA-11 PET/CT seems to be justified only in patients in whom TRUS biopsy and mpMRI could not verify malignancy despite persisting high suspicion of PC.

Primary staging

The utility of an imaging method in staging tumours depends on its power of reliably for detecting and ruling out local and distant metastases. According to current EAU (European association of Urology) guidelines, imaging modalities in newly diagnosed PC should be applied for staging mainly depending on the clinical risk for metastases and available treatment options [4]. In low-risk localised PC, no additional imaging is necessary. In patients with intermediate- to high-risk PC, multiparametric magnetic resonance imaging (mpMRI) is recommended for local tumour staging [4]. Furthermore, morphologic cross-sectional abdominopelvic imaging (CT/MRI) and bone scintigraphy should be performed in these patients for screening of metastases [4]. However, due to the limited accuracy of CT and MRI in preoperative LN staging, above all missing small LN metastases, pelvic LN dissection still remains the gold standard of LN staging in PC [41].

The advent of PET/CT scanners combining morphologic and metabolic information has prompted high hopes for the diagnostic work-up of PC. Amongst different radiopharmaceuticals investigated such as ^{18}F-FDG, ^{11}C-acetate choline-based tracers (^{18}F-choline and ^{11}C-choline) were initially considered to be quite promising in the assessment of PC. However, during the course of time, disillusioning results for initial staging of PC patients with choline PET/CT emerged regarding detection of LN metastases [42–44]. Although the sensitivity and specificity of choline PET for detection of LN metastases is higher in comparison to CT and MRI, the detection rate of LN metastases remains unsatisfactory, as demonstrated in a meta-analysis performed by Evangelista et al. showing a pooled sensitivity of only 49.2% [14]. Therefore, despite a high specificity of over 95% confirmed in several studies, choline PET/CT is not recommended as the standard imaging modality for staging PC.

With respect to the novel PET tracer ^{68}Ga-PSMA-11, very promising initial results of ^{68}Ga-PSMA-11 PET/CT in the evaluation of recurrent PC have elicited high expectations for staging PC more accurately compared to conventional staging methods. Most primary PC seem to exhibit a higher ^{68}Ga-PSMA-11 accumulation than normal prostate tissue on ^{68}Ga-PSMA-11 PET [37]. LN metastases of PC also show an overexpression of PSMA, as was observed histologically by Sweat et al. with positive immunoreactivity for PSMA in 98% of LN metastases [19]. In another histopathologic study conducted by Mannweiler et al., the majority of distant metastases revealed an overexpression of PSMA [45]. In clinical use, ^{68}Ga-PSMA-11 PET/CT has been shown to establish a method that allows detection of metastases to visceral organs and bone [31, 39, 46]. Regarding detection of PC metastases, ^{68}Ga-PSMA-11 PET/CT seems to outperform choline PET/CT. In a study comparing ^{11}C-choline to ^{68}Ga-PSMA-11 conducted by Schwenck et al. [47], in a subgroup of 20 patients referred for primary staging, significantly more LN and bone lesions consistent with metastases could be detected with ^{68}Ga-PSMA-11 PET/CT. However, it has been shown that also other tumours, such as clear cell renal cell carcinoma, glioblastoma, thyroid cancer or schwannoma, can exhibit a markedly increased tracer accumulation on ^{68}Ga-PSMA-11 PET/CT [48–51], probably due to PSMA overexpression in the neovascular structure of these tumours [22]. Therefore, histologic verification of pathologic PET findings in regions that are not commonly affected by metastases of PC is warranted to exclude second malignancies.

With respect to LN evaluation, ^{68}Ga-PSMA-11 PET/CT has been proven to identify LN metastases as small as 2.4 mm that were not judged pathologic by CT, mainly due to the size-dependent criteria for malignant LN involvement in CT [52]. In spite of this, the first results in PC patients referred to ^{68}Ga-PSMA-11 PET/CT for primary staging published by Budäus et al. were not very encouraging [53]. In a retrospective study comprising 30 newly diagnosed PC patients who underwent primary surgery, they compared LN findings of ^{68}Ga-PSMA-11 to postoperative histology after systematic pelvic LN dissection. Although specificity (100%) and the detection rate of the primary tumour (92.2%) were very good, they could only find a low sensitivity for identifying LN metastases (33.3%), missing mainly small LN metastases. They concluded that detection of LN metastases with ^{68}Ga-PSMA-11 PET/CT is limited, as sensitivity is size dependent. However, the study seems to have some limitations, e. g. pooling of patients from different institutions without standardized reports for reporting, as stated by Derlin et al. [54]. The low sensitivity in detecting LN metastases found by this group could not be confirmed by further studies with larger patient cohorts. In a retrospective study including 130 intermediate- to high-risk PC patients who underwent ^{68}Ga-PSMA-11 PET/CT or PET/MRI for primary staging, Maurer et al. could detect a much higher sensitivity for LN detection, with postoperative histology after radical prostatectomy (RP) and LN dissection serving as reference [37]. Upon patient-based and template-based analysis, they described a sensitivity of 65.9 and 68.3%, respectively. It is also noteworthy that sensitivity was significantly higher compared to simultaneously performed CT or MRI, which showed a patient- and a template-based sensitivity of only 43.9 and 27.3%, respectively, with morphological imaging alone. Similar to Budäus at al., high specificity could be observed (98.9%). These data were more or less corroborated

in a study performed by Herlemann et al. [55]. In a mixed population of PC patients, also comprising 20 patients investigated for primary staging prior to RP and lymph node dissection, Herlemann et al. described a sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT for detection of malignant LN involvement of 84 and 82%, respectively, in comparison to 65 and 76%, respectively, for CT. In a prospective trial investigating 30 patients with intermediate- to high-risk PC patients, van Leeuwen et al. again found a high specificity for detection of malignant LN involvement (95%), whereas sensitivity was 64% on a patient-based analysis, with a mean size of 2.7 mm of LN metastases that were missed by ^{68}Ga-PSMA-11 PET/CT [56].

Although ^{68}Ga-PSMA-11 PET/CT is obviously not suitable for detecting micrometastases, it seems to be superior to conventional imaging regarding detection of LN metastases. Evidence for ^{68}Ga-PSMA-11 PET/CT in primary staging of PC is still limited; however, performance of ^{68}Ga-PSMA-11 PET/CT for primary staging should be considered in PC patients with an intermediate- to high-risk of metastases, primarily for assessment of distant metastases.

Biochemical recurrence

In PC patients who present with biochemical recurrence (BR) after definitive primary therapy, early detection and exact localisation of the site of recurrence is crucial for the therapeutic decision, choice of treatment and prognosis of disease. In case of local recurrence, salvage radiotherapy (SRT) is considered most effective if PSA values are below 0.5 ng/ml [57, 58]. In patients with limited disease in whom treatment options with curative intent are considered, distant metastases should be reliably excluded. Unfortunately, currently available imaging modalities do not meet these requirements sufficiently [57, 59].

Over the past few years, highly promising data on ^{68}Ga-PSMA-11 PET/CT and its potential role in the assessment of PC patients with BR have been published. In one of the first studies addressing this issue, Afshar Oromieh et al., in a patient cohort of 319 patients with BR referred for ^{68}Ga-PSMA-11 PET/CT, 82.8% of patients showed at least one PSMA-positive lesion suggestive of PC [60]. This was confirmed in two subsequent analyses showing pathologic ^{68}Ga-PSMA-11 PET findings in 74.2 and 83% of patients with BR [31, 39]. The detection rate of pathologic lesions with ^{68}Ga-PSMA-11 PET/CT correlates with PSA value, as, for instance, was demonstrated by Ceci et al., showing a significantly higher detection rate in patients with a PSA value > 0.83 ng/ml compared to patients with a PSA value below this level (85.7 vs. 47.6%, respectively). Eiber et al. showed that the vast majority of patients with PSA levels > 1.0 ng/ml exhibited a pathologic finding on ^{68}Ga-PSMA-11 PET/CT, with a detection rate > 90% in this patient subgroup [39]. Detection rates in patients with PSA values 0.5–1.0 ng/ml in the studies performed by Afshar Oromieh at al. and Eiber et al. ranged from 58.0 to 72.7%, and most importantly, even at PSA levels < 0.5 ng/ml, the detection rate was as high as 50 and 57.9%, respectively [39, 60]. Although a clear cut-off value for performing ^{68}Ga-PSMA-11 PET/CT in patients with BR is not yet defined, its use in this setting seems to be justified even at PSA levels lower 0.5 ng/ml.

Choline PET/CT, using either ^{11}C- or ^{18}F-labelled choline, has limited sensitivity in this setting. Collating results of ^{68}Ga-PSMA-11 PET/CT with published data on choline PET/CT [11–13, 16, 17], ^{68}Ga-PSMA-11 PET/CT seems to outperform choline PET/CT, especially at low PSA levels. In a comparative study of ^{18}F choline versus ^{68}Ga-PSMA-11 PET/CT comprising 38 patients with BR, in whom SRT was planned, Morigi et al. could demonstrate a significantly higher detection rate with ^{68}Ga-PSMA-11 compared to ^{18}F-choline [61]. Above all, in the subgroup of patients with PSA values < 0.5 ng/ml, the results were impressive, as ^{68}Ga-PSMA-11 PET/CT was judged positive in 50% of patients compared to only 12.5% on ^{18}F-choline PET/CT. What is noteworthy is that in 75% of ^{68}Ga-PSMA-11-positive patients in whom SRT of the prostatic bed was planned, ^{68}Ga-PSMA-11 could detect ^{68}Ga-PSMA-11-positive lesions outside the prostatic fossa. An example of direct comparison between ^{68}Ga-PSMA-11 PET/CT and ^{18}F-choline PET/CT in a patient with BR is given on Fig. 1.

In a head-to-head comparison of ^{68}Ga-PSMA-11 PET and diagnostic CT, including 248 PC patients with BR, a retrospective trial performed by BR Eiber et al. revealed a substantial contribution of ^{68}Ga-PSMA-11 PET in a significant number of patients compared to CT alone [39]. In 32.7% of patients, the site of relapse was found with ^{68}Ga-PSMA-11 PET although it was not detected with CT alone, whereas in only 1.2% of patients, CT was exclusively positive. Furthermore, in those patients in whom recurrent lesions could be found with both modalities, additional clinically relevant lesions suggestive of PC were found solely with PET in 24.6% of cases, compared to 6.9% of supplementary findings suspicious of metastases with diagnostic CT. Thus, in more than 50% of cases, ^{68}Ga-PSMA-11 PET provided information that was judged relevant for therapy which was not seen by CT.

In a study including 70 patients with BR scheduled for SRT, Van Leeuwen et al. could demonstrate a major change in therapy in 28.6% of patients based on the results of ^{68}Ga-PSMA-11 PET/CT [62].

Besides PSA level, PSA doubling time (PSAdt) seems to be a significant predictor for PET positivity. As already indicated by Ceci et al. [31], and subsequently confirmed by Verburg et al., shorter PSAdt is associated with a higher probability of a positive finding on ^{68}Ga-PSMA-11 PET/CT. Furthermore, patients with a shorter PSAdt exhibited a significantly higher rate of ^{68}Ga-PSMA-11-positive lesions consistent with malignant LN involvement and distant metastases [63].

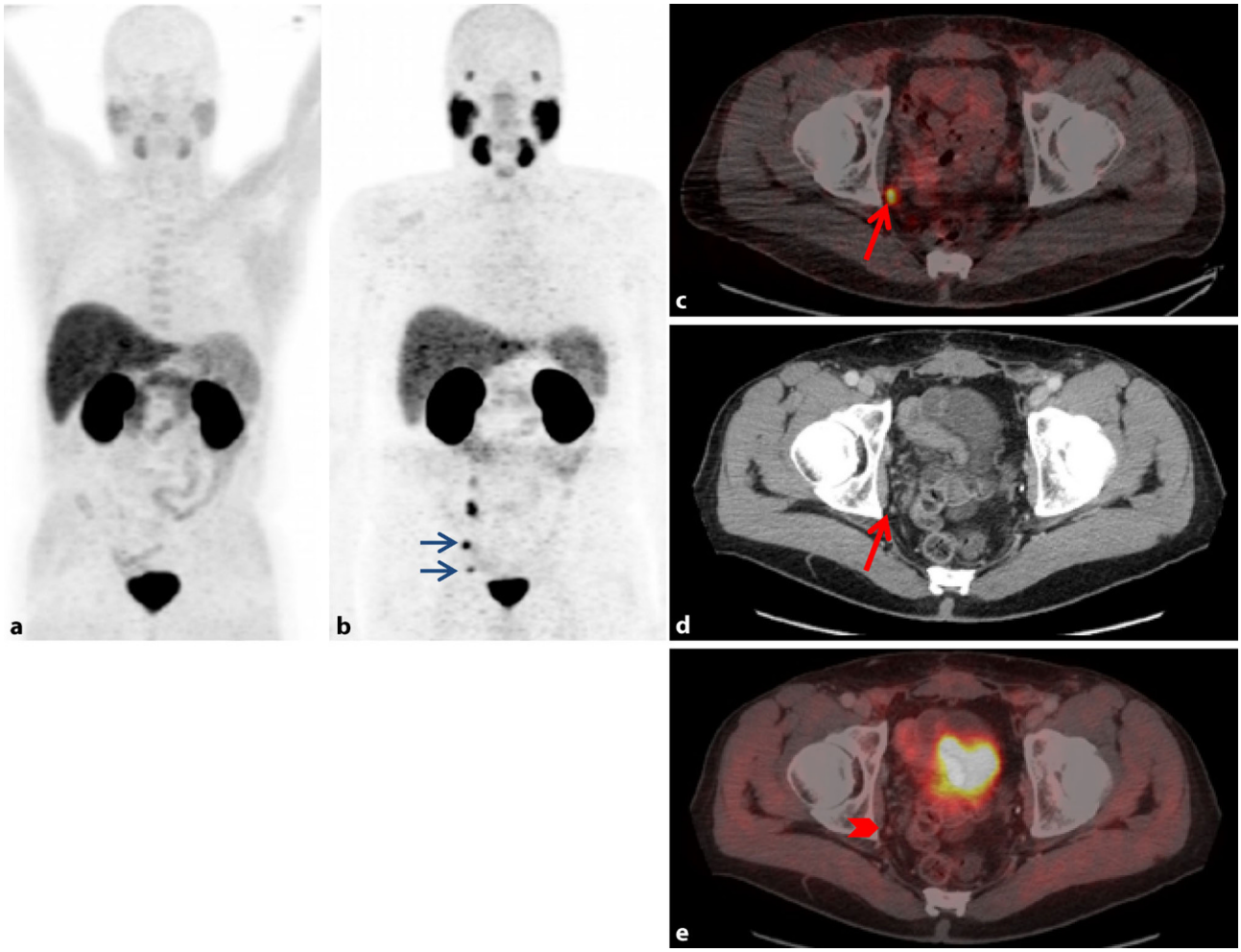

Fig. 1 Comparison of ^{18}F-choline PET/CT (contrast enhanced CT) and ^{68}Ga-PSMA-11 PET/CT (low-dose CT) in a 64-year-old PC patient with biochemical recurrence after radical prostatectomy (PSA at time of choline PET: 3.41 ng/ml): ^{18}F-choline PET/CT did not reveal a pathologic finding, as displayed on maximum-intensity projection (MIP, **a**). In contrast, on ^{68}Ga-PSMA-11 PET/CT performed 3 weeks later, two pathologic lesions in the right pelvis were found (**b**; *blue arrows*), corresponding to two LN on CT. One LN with an axial diameter of 5.7 mm is displayed on fused axial (**c**) and CT images (**d**), marked with a *red arrow*. On fused axial ^{18}F-choline PET/CT images, no pathologic uptake could be detected in the LN (**e**; *red arrow head*). The two lesions with markedly increased uptake of ^{68}Ga-PSMA-11 PET seen on MIP in the right lower abdomen (**b**) correlated with physiologic tracer activity in the ureter. *CT* computed tomography, *PET* positron emission tomography, *PSMA* prostate specific membrane antigen, *PSA* prostate specific antigen, *LN* lymphnode

According to the data by Verburg et al., patients with a PSAdt of <6 months seem to profit most from performing a ^{68}Ga-PSMA-11 PET examination.

Regarding assessment of malignant LN involvement, in a retrospective study with 21 PC patients evaluated for BR, Giesel et al. found a significantly higher sensitivity for detection of pathologic LN compared to CT. 78% of ^{68}Ga-PSMA-11-positive LN were not judged pathologic on CT, mainly due to a size smaller than 8 mm [52], resulting in an upstaging of two thirds of patients from cN0 to N1 after PET imaging. The potential benefit of ^{68}Ga-PSMA-11 PET in staging LN in PC patients in comparison to morphology-based imaging techniques was underlined in another study by Freitag et al. [33]. 71.9% of LN that showed a pathologic tracer accumulation on ^{68}Ga-PSMA-11 PET were normal sized on CT and MRI. However, in neither study was verification of PET-positive results with postoperative histology performed.

A recently published study Rauscher et al. compared PET LN findings to postoperative histology in 48 patients with BR who underwent salvage lymphadenectomies. The specificity of ^{68}Ga-PSMA-11 PET and simultaneously performed morphologic imaging (CT and MRI) was almost identical, with 97.3 and 99.1%, respectively. However, ^{68}Ga-PSMA-11 performed significantly better in correctly identifying LN metastases, with a sensitivity of 77.9% compared to only 26.9% with CT and MRI. ^{68}Ga-PSMA-11 PET could detect smaller sized LN metastases in comparison to CT/MRI with a mean size of 8.3 mm and 13.0 mm, respectively [64].

Apart from evaluation of local tumour spread, ^{68}Ga-PSMA-11 PET/CT also has the power to detect distant

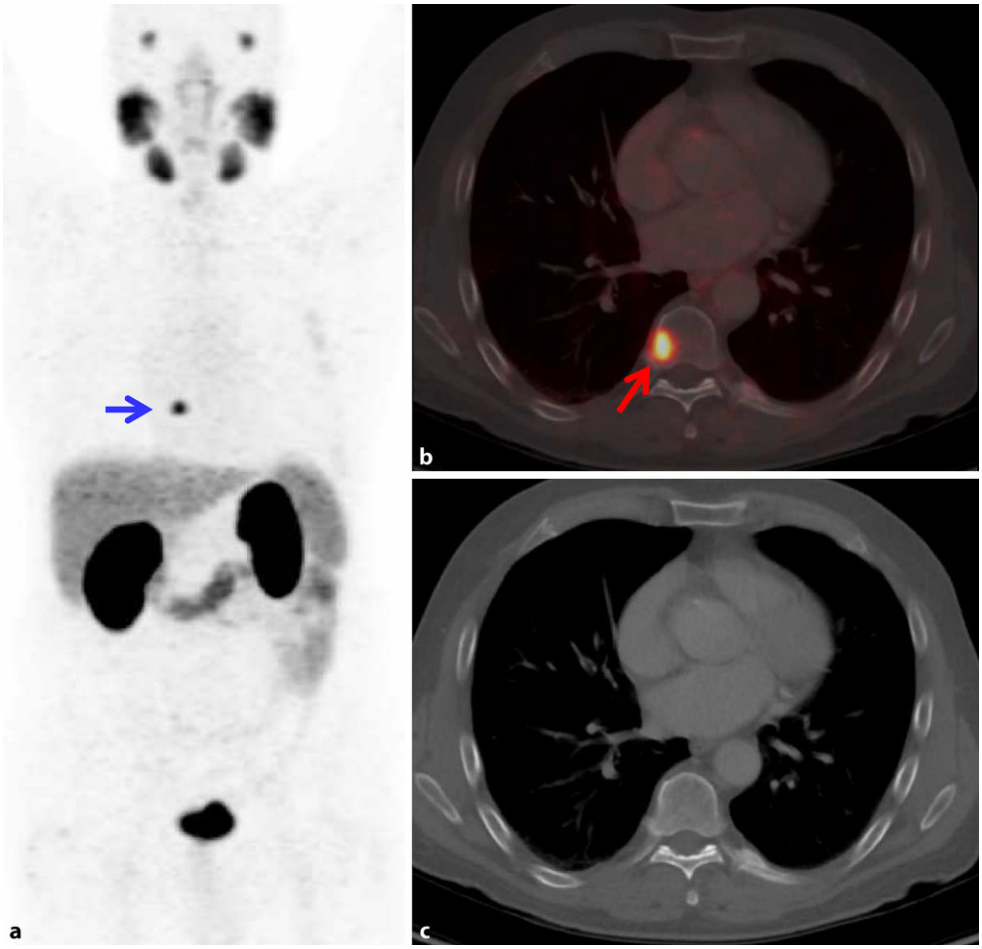

Fig. 2 ^{68}Ga-PSMA-11 PET/CT of a 71-year-old PC patient with biochemical relapse (PSA: 1.0 ng/ml) after radical prostatectomy. On maximum-intensity projection image, a pathologic focal uptake is seen in the thoracic area (**a,** *blue arrow*). On fused axial images (**b**), the lesion is projected in a vertebral body of the thoracic spine (*red arrow*). On CT (**c**), a faint osteolytic area, which was not described initially, could be detected only after comparison with PET images. No other site of recurrence was found. *PSMA* prostate specific membrane antigen, *PET* positron emission tomography, *CT* computed tomography, *PSA* prostate specific antigen

metastases, as shown, for instance, in the two studies by Ceci et al. and Eiber et al. [31, 39]. They reported detection rates of ^{68}Ga-PSMA-11-positive tumour lesions consistent with distant metastases in 11.4 and 41.1% of cases, respectively. The majority of lesions were confined to the bone, but pathologic lesions in other tissues such as lung and liver were also found. In this context, bone scintigraphy, especially performed in a planar mode without application of SPECT(single photon emission tomography)/CT, is known to be quite insensitive in detecting bone metastases that are small in size or mainly osteolytic [6, 7, 65, 66]. Diagnostic contrast-enhanced CT also has limitations with respect to assessment of malignant bone involvement, above all missing bone marrow infiltration, as also demonstrated in PC patients [67, 68]. Furthermore, given that small bone metastases may be overlooked on CT, combined PET/CT seems to be advantageous, with the PET component sometimes serving as marker and guide for identification of metastases on CT images, as highlighted by the case in Fig. 2.

One major limitation of all studies dealing with the role of ^{68}Ga-PSMA-11 PET/CT in evaluating PC patients with BR published so far is the lack of correlation of pathologic PET findings with histology in a sufficient number of patients. Despite this fact, the results of histologic verification in the limited number of cases published to date indicate that at least the true positive rate and specificity of ^{68}Ga-PSMA-11 PET/CT is relatively high, with hardly any false-positive PET findings confirmed by histopathology [31, 39, 64, 69].

Although the currently available data allow the conclusion that ^{68}Ga-PSMA-11 PET/CT seems to constitute a very sensitive method in detecting recurrent PC lesions in patients with BR, influencing patient management decisively, there is a need for prospective trials comparing PET findings to postoperative histology to confirm these promising results. However, to summarize, application of ^{68}Ga-PSMA-11 PET/CT appears to be justified at least in patients in whom a curative treatment option is considered (e. g. SRT).

Evaluation of therapy response

Although evaluation of treatment response with ^{68}Ga-PSMA-11 PET/CT seems possible, at present, its use in this indication is not recommended, due to missing data addressing this issue. In this context, from a nuclear medicine perspective, PC patients with metastatic disease referred to palliative treatment of bone metastases with ^{233}radium dichloride could

constitute one possible indication for a ^{68}Ga-PSMA-11 PET/CT scan. Visceral metastases must be reliably excluded before initiation of therapy with this new agent. On the other hand, conventional bone scintigraphy and also NaF-PET might show a "flare-phenomenon", due to a response to therapy that frequently cannot be differentiated from disease progression [66]. In contrast, for ^{68}Ga-PSMA-11 PET/CT, no flare phenomenon has been described to date.

Conclusion

During the past few years, the successful introduction of PSMA ligands suitable for PET/CT imaging has caused high expectations in the societies of nuclear medicine and urology regarding the diagnostic work-up of PC patients. Although several studies with the most widely applied PSMA ligand ^{68}Ga-PSMA-11 in clinical practice have indicated that this novel tracer seems to be a powerful tool for detecting PC lesions, the new technique has not yet entered generally accepted guidelines for PC management. For definitive assessment of the role of ^{68}Ga-PSMA-11 PET/CT, prospective trials in large patient cohorts combined with preferably histologic verification of pathologic PET findings are necessary, in order to confirm the promising, albeit mainly retrospectively acquired data. Despite this major limitation, the rising star ^{68}Ga-PSMA-11 has the potential to become a fixed star on the firmament of useful diagnostic procedures applied in PC patients. Based on the currently available results, performance of ^{68}Ga-PSMA-11 PET/CT appears to be justified in PC patients with BR with curative treatment option, in primary staging of patients with a high risk for metastases (GS > 7 and PSA > 10 ng/ml) and in patients with a high suspicion of PC, in whom TRUS biopsy and mpMRI could not detect a tumour.

Conflict of interest C. Uprimny declares that he has no competing interests.

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