Gallium-68 Prostate-Specific Membrane Antigen PET Imaging

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KEYWORDS

• Prostate cancer • Prostate-specific membrane antigen • PET • ^{68}Ga-PSMA • ^{68}Ga-PSMA PET

KEY POINTS

- Gallium-68 (^{68}Ga) prostate-specific membrane antigen (^{68}Ga-PSMA) imaging has superior accuracy to conventional imaging modalities, including choline PET/computed tomography (CT).
- ^{68}Ga-PSMA imaging can be used in the context of high-risk localized prostate cancer (PCa), by defining the extent of primary, regional, and distant metastases; prostate-specific antigen (PSA) recurrence; the location of PCa lesion even in the low level of PSA; and of oligometastatic disease and by determining the extent of disease to guide the therapy.
- Imaging specialists need to familiarize themselves with physiologic ^{68}Ga-PSMA uptake, common variants, pattern of locoregional and distant spread of PCa, and its inherent pitfalls; they should also educate the clinicians about the capabilities and limitations of this imaging modality.

INTRODUCTION

Prostate cancer (PCa) is one the most common malignancies in men worldwide and leads to substantial morbidity and mortality. Imaging of PCa is indicated for primary diagnosis, staging, and restaging as well as for localization of recurrent disease. Currently, conventional imaging modalities, including ultrasound, bone scintigraphy, CT, and MR imaging, are used to detect primary and metastatic PCa for staging and risk stratification. Despite significant efforts, conventional imaging of PCa does not contribute to patient management as much as imaging performed in patients with other common cancers.

The main limitation of conventional imaging modalities is their low sensitivity in detecting metastases in primary diagnosis or in recurrent PCa, in particular with low PSA levels when disease is often small in volume. In a meta-analysis of 24 studies, the pooled sensitivity and specificity of CT for lymph node diagnosis were 42% and 82%, respectively. For MR imaging, this review reported the pooled sensitivity and specificity of 39% and 82%, respectively.[1] Although functional assessment of the disease with additional MR sequences, such as diffusion-weighted MR imaging or dynamic contrast-enhanced MR imaging, are increasingly used for imaging of PCa, these

imaging techniques suffer from nontumor specificity and a lack of high-level evidence for their utility.

Molecular imaging with PET using an increasing list of biologically relevant radiotracers is facilitating the precision and personalized medicine in PCa.[2] PSMA has received a resurgence of attention over the past few years as a useful biomarker in the imaging of PCa. Among the available tracers and ligands available to image PSMA-expressing tumors, Glu-NH-CO-NH-Lys-(Ahx)-[[68]Ga(HBED-CC)], also known as ^{68}Ga-PSMA HBED-CC or ^{68}Ga-PSMA-11, developed by the Heidelberg group in Germany, became one of the most successful and promising PSMA radioligands and demonstrated a rapid spread across many countries.[3–5]

RADIOLABELED PROSTATE-SPECIFIC MEMBRANE ANTIGEN LIGANDS

PSMA is a type II, integral membrane glycoprotein that was first detected on the human prostatic carcinoma cell line LNCaP.[6] It consists of 750 amino acid integral membrane glycoprotein (100–120 kDa), with a 19–amino acid intracellular component, a 24–amino acid intramembrane segment, and a large 707–amino acid extracellular domain.[7] It has several enzymatic functions and is known to be up-regulated in castrate-resistant and metastatic PCa.[8] PSMA is not specific to the prostate gland and is expressed in other normal tissues, including salivary glands, duodenal mucosa, proximal renal tubular cells, and subpopulation of neuroendocrine cells in the colonic crypts. In PCa, PSMA is overexpressed approximately 100 times to 1000 times compared with normal prostate tissue.[9] It is also overexpressed in multiple other neoplasms (eg, subtypes of transitional cell carcinoma, renal cell carcinoma, colon carcinoma, and peritumoral and endotumoral endothelial cell of neovasculature).[10] There is no known natural ligand for PSMA and the reasons for its up-regulation in PCa remains unclear. PSMA undergoes constitutive internalization and as such can serve not only as an imaging biomarker but also for targeted therapy – in other words, PSMA may be useful as a target for theranostic agents.[11]

In malignant tissue, PSMA has been suggested as involved in angiogenesis, because increased PSMA expression was found expressed in the stroma adjacent to neovasculature of solid tumors.[12] Due to its selective overexpression in 90% to 100% of local PCa lesions, as well as in cancerous lymph nodes and bone metastases,[13–15] PSMA is a reliable tissue marker for PCa and is considered an ideal target for theranostic applications.[16–19]

Increased PSMA expression is correlated with an increase in tumor grade, pathologic stage, aneuploidy, and biochemical recurrence. Of clinical importance is that PSMA expression is up-regulated when tumors become androgen independent and also after antiandrogen therapy (ADT) in most cases.[20] This characteristic makes PSMA particularly valuable, because it has potential as an early indicator of tumor progression after ADT and could play a role as a prognostic factor for disease recurrence.[21]

One of the first imaging probes specifically targeting PSMA was indium-111 (^{111}In) capromab pendetide (ProstaScint), a ^{111}In-labeled anti-PSMA antibody.[22] An important limitation of capromab pendetide is that it binds to an intracellular epitope of the transmembrane PSMA glcyoprotein. Therefore, capromab pendetide either binds to viable tumor cells after internalization or to dying cells with disrupted cellular membranes. Furthermore, slow plasma clearance of the antibody results in poor tumor-to-background contrast, the application of ^{111}In–capromab pendetide for imaging prostatic malignancies remained limited.[23,24]

Subsequently, high-affinity antibodies directed against extracellular epitopes of PSMA have been developed, such as J415, J533, and J591.[25] It was shown that ^{111}In-J591 accurately targets bone and soft tissue metastatic PCa lesions[26] and that lutetium-177 (^{177}Lu)-labeled J591 can be used safely in radioimmunotherapy directed against micrometastatic PCa.[27] Major disadvantages limiting the use of radiolabeled monoclonal antibodies as theranostic radiopharmaceuticals are their long circulatory half-life (3–4 days), poor tumor penetration, and low tumor-to-normal tissue ratios, especially at early time points. Small molecules, in contrast, exhibit rapid extravasation, rapid diffusion in the extravascular space, and faster blood clearance. This could result in high tumor-to-normal tissue contrast early after injection of the tracer.

In search for PSMA tracers with such favorable characteristics, modified forms of N-acetylated-a-linked acidic dipeptidase (NAALAdase) inhibitors, which were originally developed for possible neuroprotective effects in neurologic disorders, such as amyotrophic lateral sclerosis,[28] have been evaluated for their potential to diagnose and treat PCa. A series of preclinical studies evaluated the role of radiolabeled small-molecule PSMA-inhibiting ligands for imaging of human PCa using various radionuclides, such as carbon-11 (^{11}C),[29] fluorine-18 (^{18}F),[30] iodine-123 (^{123}I),[31] technetium-99m (^{99m}Tc),[32,33] and [68]Ga.[34,35] Overall, the PSMAs tested in these preclinical studies showed high tumor uptake peaking at 0.5 hour to 1 hour in mice with

PSMA-expressing tumors. At earlier time points, the contrast was impaired due to high blood levels. For imaging purposes, this time frame matches best with radionuclides with half-lives of 1 hour to 2 hours (ie, ^{68}Ga or ^{18}F). In some of these pre-clinical studies, remarkable changes in affinity and tumor uptake were observed on changes in the radiolabel, chelator, and linker. First of all, it has been suggested that a spacer is required between the PSMA binding motif and the chelator. Chen and colleagues[36] have compared PSMAs with different linker lengths and showed that an increased linker length enhanced the affinity for PSMA and increased tumor uptake.

Since 2012, the number of clinical studies using urea-based PSMAs, such as $^{123/124/131}$IMIP-1072/-1095,[37] ^{99m}Tc-MIP-1404/-1405,[38] ^{68}Ga-HBED-PSMA, ^{18}F-DCFBC,[39] and ^{18}F-DCFPyl, exponentially increased.[4,40–42] Among these agents, the ^{68}G-lableled and ^{18}F-labeled compounds have attracted the most attention, because these compounds can be used for PET/CT imaging. The availability of ^{123}I or ^{99m}Tc, however, allows single-photon emission CT (SPECT)/CT imaging in centers without facilities for PET.

PET/COMPUTED TOMOGRAPHY IMAGING WITH GALLIUM-68 PROSTATE-SPECIFIC MEMBRANE ANTIGEN

During the past few years, the application of ^{68}Ga-labeled peptides has attracted considerable interest for cancer imaging due to the physical characteristics of ^{68}Ga (half-life of 68 minutes, beta decay of 1899 keV)[43] and the availability of reliable germanium-68 (^{68}Ge)/^{68}Ga generators. This enabled ^{68}Ga-DOTATATE PET/CT imaging of neuroendocrine tumors,[44,45] owing to the rapid binding and cellular uptake of DOTATATE, and this is now widely recognized as the new gold standard for imaging these tumors. Moreover, the half-life of ^{68}Ga is suitable for the pharmacokinetics of the small PSMA-inhibiting peptides, which have rapid binding and cellular uptake. Among the first PSMA inhibitors available for labeling with ^{68}Ga and PET imaging of PCa were 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) conjugated urea-based PSMA inhibitors, developed and tested preclinically by Banerjee and colleagues.[34] Eder and colleagues[46] prepared the ^{68}Ga-PSMA inhibitor Glu-NH-CO-NHLys(Ahx)-HBED-CC using the chelator N,N'-bis[2–hydroxy-5-(carboxyethyl)-benzyl]ethylene diamineN,N'-diacetic acid (HBED-CC). Potentially, HBED is a more attractive chelator for ^{68}Ga than DOTA because it forms a more thermodynamically stable complex with ^{68}Ga, even at room temperature.[47] Eder and colleagues[46] compared Glu-NH-CO-NHLys(Ahx)-HBED-CC with Glu-NH-CO-NH-Lys-DOTA and demonstrated that the HBED-CC conjugated compound had more favorable properties for PCa imaging than the DOTA analog. ^{68}Ga-labeled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (^{68}Ga-PSMA) showed fast blood clearance, low liver uptake, and high specific uptake in PSMA-expressing tissues and tumor (tumor uptake 7.7% $\pm$ 1.5% injected dose (ID)/g for the HBED-CC conjugate, which was 2.6-fold higher compared with the DOTA compound). In addition, liver uptake of the HBED-CC conjugated ligand was 5.7-fold lower (**Fig. 1**).

Based on the promising preclinical results, the German Cancer Research Center in Heidelberg performed the first clinical investigation of the ^{68}Ga-PSMA in a cohort of 37 patients. In 84% of the patients, PCa lesions were identified.

Fig. 1. Maximum intensity projection image demonstrates physiologic distribution of ^{68}Ga-PSMA with highest intensity of uptake in the kidneys, excreted urine in the bladder and salivary glands.

PCa lesions were found in 60% of the patients with PSA levels less than 2.2 ng/mL, whereas at PSA levels of greater than 2.2 ng/mL, PCa lesions were found in all patients. Thus, even at low blood PSA levels, ^{68}Ga-PSMA PET/CT identified lesions with high tumor-to-background ratios. Tumor uptake of ^{68}Ga-PSMA was stable between 1 hour and 3 hours, whereas in normal tissue, uptake slightly decreased between 1 hour and 3 hours. As a result, late scans exhibited higher tumor-to-background ratios, which might be useful when lesions remain unclear in an early scan.[4] In a more recent study by this group, imaging with ^{68}Ga-PSMA PET/CT was performed at 5 minutes, 1 hour, 2 hours, 3 hours, 4 hours, and 5 hours after injection in patients with recurrent PCa. Most of tumor lesions were visible at 3 hours post injection, whereas at all other time points many were not qualitatively present; therefore, they concluded that this time point would be optimal for imaging.[48] Since this study, there has been increasing number of studies investigating ^{68}Ga-PSMA in the different aspects of PCa.

Gallium-68 Prostate-Specific Membrane Antigen in Biochemical Recurrence After Radical Treatment of Prostate Cancer

Biochemical relapse after radical prostatectomy or radiotherapy occurs in up to half of patients with PCa.[49] More than a quarter of patients with biochemical recurrence eventually develop clinical recurrence in approximately 7 years to 8 years.[49] Detection of the sites of recurrent disease is of paramount importance because this avoids futile localized treatment in cases and systemic recurrence and avoids the side effects of systemic treatments in cases of localized recurrence (Fig. 2). One of the major drivers in detecting very low volume disease in the recurrent setting is the feasibility of treating oligometastatic disease with technologies, such as stereotactic radiotherapy, and in doing so potentially obtaining a further clinical/biochemical remission.[50] Whether this approach improves long-term patient outcomes, however, is yet to be established.

The diagnostic yield of conventional imaging modalities for local recurrence and lymph node and bone metastasis after radical prostatectomy
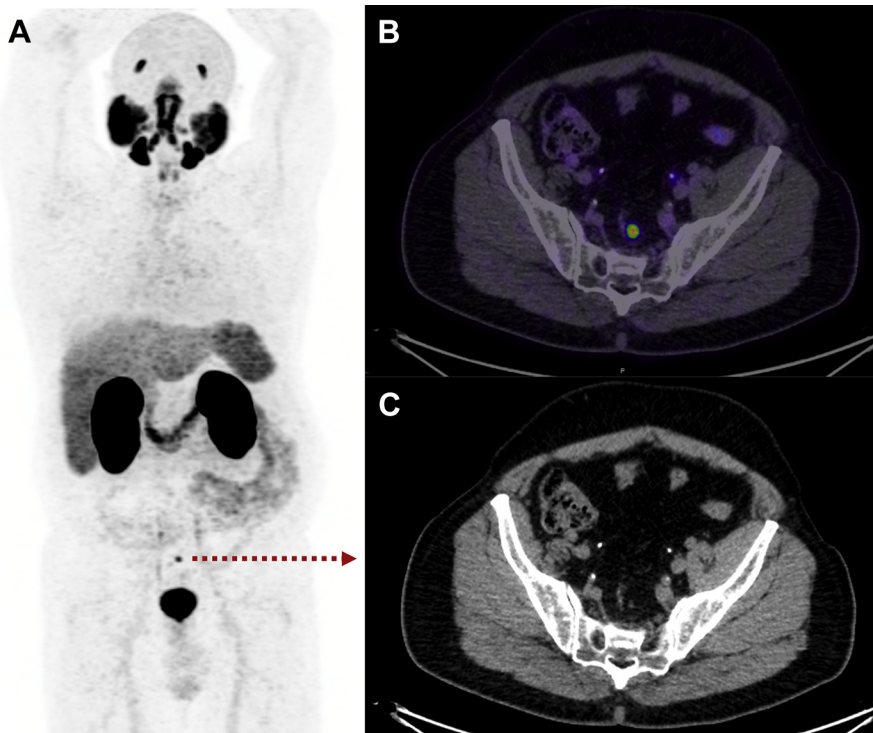

Fig. 2. PSMA PET maximum intensity projection image (*A*) of a patient with biochemical recurrence after radical prostatectomy with PSA of 0.34 ng/mL, demonstrates focal uptake in the pelvis (*arrow*). PET/CT images (*B, C*) show uptake in a small presacral lymph node.

is low. Bone scan (BS) has detection rate of less than 5% for PSA values of less than 7 ng/mL.[49] Similarly CT has low sensitivity (11%–14%) in predicting lymph node and local recurrence in this cohort of patients.[49] 68Ga-PSMA PET imaging has had its most promising outcomes in patients with recurrent PCa and its ability to detect metastatic disease at very low volume disease and low PSA levels.

Gallium-68 prostate-specific membrane antigen detection rate and its relation to prostate-specific antigen level

Afshar-Oromieh and colleagues[51] retrospectively investigated the diagnostic value of 68Ga–HBED-CC–PSMA PET/CT in 319 patients with PCa. 68Ga-PSMA PET/CT detected PCa in 83% of the patients suspected recurrent PCa (264 of 319 patients). In addition, the tracer is highly specific for PCa: histologic analysis demonstrated that tracer accumulation in tumor lesions correlated with manifestations of PCa in virtually all cases without false-positive lesions. Eiber and colleagues[52] reported the diagnostic accuracy of 68Ga–HBED-CC–PSMA PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. In this study, 222 patients (89.5%) showed pathologic findings in 68Ga–HBED-CC–PSMA PET/CT. Positive correlation was found between the PSA level and PSMA PET/CT detection rate. The detection rates were 96.8%, 93%, 72.7%, and 57.9% in patients with serum PSA-levels of greater than or equal to 2.1 ng/mL, less than 2.0 ng/mL to 1.0 ng/mL, less than 1.0 ng/mL to 0.5 ng/mL, and less than 0.5 ng/mL to 0.2 ng/mL, respectively.[52]

In a meta-analysis performed by Perera and colleagues,[53] including 16 articles and 1309 patients, the overall percentage of positive 68Ga-PSMA PET was 76% for biochemical recurrence. The detection rate for the PSA categories 0 to 0.2, 0.2 to 1, 1 to 2, and greater than 2 ng/mL were 42%, 58%, 76%, and 95% scans, respectively. On per-patient analysis, the sensitivity and specificity of 68Ga-PSMA PET were both 86% whereas on per-lesion analysis, the sensitivity and specificity were 80% and 97%, respectively.[53]

Comparison between gallium-68 prostate-specific membrane antigen and radiolabeled choline PET

68Ga-PSMA showed substantially higher detection rates compared with choline ligand PET/CTs with the detection rates between 34% and 88% for 11C-choline, 43% to 79% for 18F-choline, and 59% to 80% for 11C-acetate.[54] Bluemel and colleagues[55] investigated the value of 68Ga-PSMA

PET/CT in biochemically recurring PCa patients with negative 18F-choline PET/CT. With the sequential imaging approach, Ga-PSMA PET identified sites of recurrent disease in 43.8% of the patients with negative F-choline PET scans. Subgroup analysis of Ga-PSMA PET in 18F-choline–negative patients revealed detection rates of 28.6%, 45.5%, and 71.4% for PSA levels of 0.2 ng/mL to 1 ng/mL, 1 ng/mL to 2 ng/mL, and greater than 2 ng/mL, respectively.[55]

Comparison between gallium-68 prostate-specific membrane antigen and histologic assessment and morphologic imaging

There is a paucity of data comparing between 68Ga-PSMA findings and histologic assessment. Rauscher and colleagues[56] investigated the accuracy of the 68Ga-PSMA PET/CT compared with morphologic imaging (CT or MR imaging) in 48 patients with biochemical recurrence of PCa who underwent salvage lymphadenectomy. The specificity of 68Ga-PSMA PET was 97% compared with 99% morphologic imaging. PET, however, detected 78% of histopathologic proved lymph node, whereas morphologic imaging was positive in only 27%. Diagnostic accuracy of 68Ga-PSMA PET imaging was, therefore, 90% and for morphologic imaging 72%. The mean short axis size of 68Ga suspicious lymph node on PET was 8.3 mm $\pm$ 4.3 mm compared with 13.0 mm $\pm$ 4.9 mm for suspicious nodes identified on morphologic imaging alone. Histopathologic assessment of false-negative lymph node fields in 68Ga-PSMA HBED-CC PET revealed a mean lesion size of 4.7 $\pm$ 3.4 mm (range: 0.5–11 mm).[56] In another study performed by Giesel and colleagues[57] comparing the lymph node detection rates between 68Ga-PSMA-based PET/CT imaging and 3-D CT volumetric lymph node assessment in 21 patients with intermediate-risk and high-risk PCa patients who had biochemical recurrence after radical prostatectomy, 68Ga-PSMA PET/CT was more sensitive than volume-based CT evaluation of lymph node recurrence, with PET detecting nodal recurrence in two-thirds of patients who would have otherwise been missed by CT evaluation.

Afshar-Oromieh and colleagues[40] reported initial experience of 68Ga-PSMA PET/CT compared with PET/MR imaging. In this study, 20 patients were scanned with PET/CT and PET/MR imaging sequentially. Of the 75 lesions that were characterized further, 4 lesions unclear in PET/CT could be established as PCa lesions in PET/MR imaging. Pathologic lesions visible on PET often correlated with signals on MR imaging, offering a considerable advantage for

PET/MR imaging. Overall, PCa was detected more easily and more accurately with ^{68}Ga-PSMA PET/MR imaging than with PET/CT. A potential disadvantage of PET/MR imaging, however, was the appearance of halo artifacts around the bladder and kidneys, resulting in a reduced PET signal, potentially making lesions in their vicinity undetectable.[40]

Factors affecting gallium-68 prostate-specific membrane antigen detection rate

Although it has been shown that the diagnostic value of ^{68}Ga-PSMA PET/CT in patients with PCa is high, even in patients with low PSA serum levels and compared with other tracers, such as radiolabeled choline, approximately 40% of the patients with PSA levels of less than 0.5 ng/mL showed negative ^{68}Ga-PSMA PET/CT results.[51] Therefore, Ceci and colleagues[58] evaluated which factors are associated with the ^{68}Ga-PSMA PET/CT tumor lesion detection rate. In this study, 70 patients with recurrent PCa underwent ^{68}Ga-PSMA PET/CT and were retrospectively evaluated regarding their previous therapies, serum PSA levels, PSA doubling times, and PSA velocity. A serum PSA level of 0.83 ng/mL and a PSA doubling time of 6.5 months were found valuable cutoff values for predicting, with high probability a positive or negative scan result. In particular, 85% of patients with short PSA doubling times who were candidates for radiotherapy to the prostate bed (early phase of biochemical recurrence with low PSA levels) showed positive findings on PET/CT, whereas only 18.7% of patients with similar low PSA levels but with long PSA doubling time were PET positive.[58]

Gallium-68 Prostate-Specific Membrane Antigen in the Lymph Node Staging Prior to Radical Prostatectomy

Due to the low accuracy of current imaging modalities for lymph node staging, clinicians are reliant on preoperative models using PSA levels, Gleason score (GS), and T stage to dictate lymphadenectomy protocols.[59] Lymphadenectomy may add significant morbidity to the radical prostatectomy procedure and more accurate staging may enable management change. The evidence favoring ^{68}Ga-PSMA PET imaging for detection of lymph node metastasis in this cohort of patients is evolving. Eiber and colleagues[60] prospectively evaluated ^{68}Ga-PSMA PET imaging for preoperative lymph node staging in 37 intermediate-risk and high-risk patients undergoing radical prostatectomy and extended pelvic lymph node dissection. In the PET-positive cohort (33/37), on patient-based analysis, sensitivity and specificity

were 75% and 96%, respectively. On field-based analysis, the sensitivity and specificity were 65% and 98%, respectively.[60] In the PET-negative patients (4/37), 2 patients had false-negative results. In a recent retrospective series, Budaus and colleagues[61] reported less promising results with overall sensitivity, specificity, positive predictive value, and negative predictive value of ^{68}Ga-PSMA PET/CT for lymph node metastasis detection of 33%, 100%, 100%, and 69%, respectively. This group hypothesized that in primary staging a significant proportion of the PSMA is taken up by the prostate, as a result limiting its availability in the lymph nodes.[61] Other suggestions for the less impressive outcomes were restricted perfusion in lymph node metastasis due to a critical size or vascularization threshold, variable expertise, and small sample size.[61]

Gallium-68 Prostate-Specific Membrane Antigen in Local Staging of the Prostate Cancer

There are few data on the role of ^{68}Ga-PSMA PET imaging in primary local staging of PCa. PCa patient risk is determined by considering several factors, including PSA level and GS. Various imaging techniques have been used for local staging and biopsy guidance. In particular, multiparametric MR imaging shows promising results for localizing PCa and improving accuracy of transrectal ultrasound biopsy.[62,63] Despite significant effort in standardization of reporting, the major drawback of MR imaging remains significant interobserver variability resulting in heterogeneous reported accuracy in the literature.[64] Furthermore, MR imaging performance in low-volume disease and identifying extraprostatic extension of cancer is less impressive.[65] Additional molecular information and higher tumor-to-background ratio, however, provided by ^{68}Ga-PSMA PET could potentially overcome this inadequacy and further refine the targeting of lesions[66] (**Fig. 3**).

In a recent study, Fendler and colleagues[67] evaluated the accuracy of ^{68}Ga-PSMA PET/CT in localizing PCa at initial diagnosis in 21 patients. This study demonstrates promising accuracy with high positive predictive value in excess of 95%. On segment-based analysis, however, the sensitivity of PSMA PET was moderate (67%), which still was higher than pooled sensitivity (54%–66%) of various MR imaging protocols in a systematic review.[68] Furthermore, ^{68}Ga-PSMA PET had high (86%) accuracy for the detection of seminal vesicle involvement.[67]
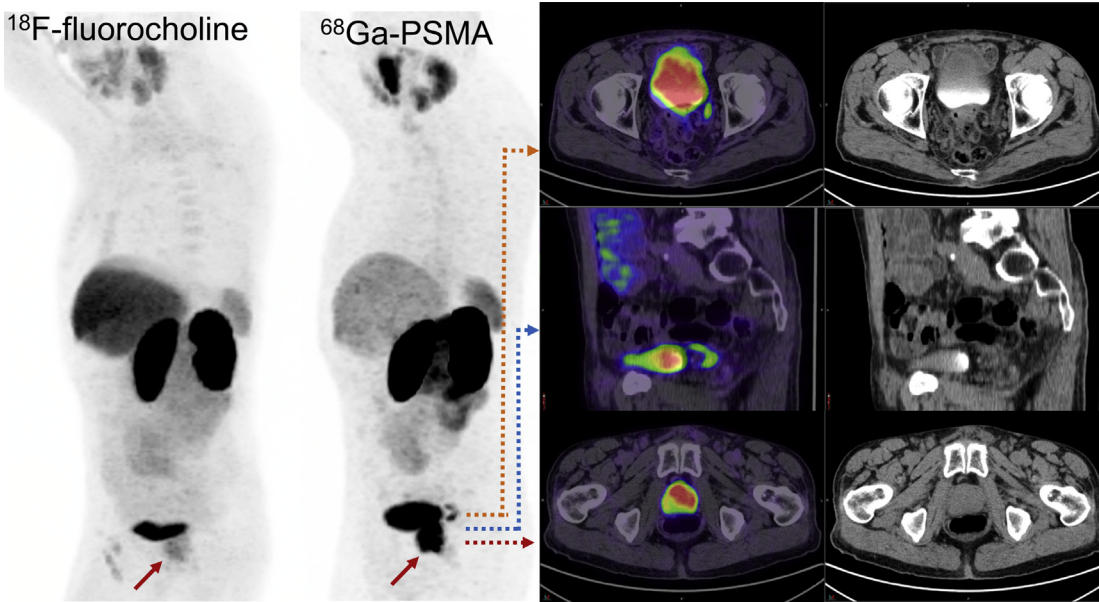
Fig. 3. (*Left*) Fluorocholine PET MIP (oblique projection) image of a 70-year-old man with GS 9 PCa and PSA of 100 ng/mL demonstrates mildly avid primary prostate cancer (*solid red arrow*). (*Right*) PSMA PET MIP image and corresponding PET/CT images show intensely PSMA expressing locally advanced prostate cancer (*dashed red arrow*) with extension of tumor along the seminal vesicle (*dashed blue arrow*) and vas deference (*dashed orange arrow*).

Gallium-68 Prostate-Specific Membrane Antigen PET and Response Assessment

Response assessment in metastatic PCa is often suboptimal due to limited applicability of Response Evaluation Criteria in Solid Tumors version 1.1 criteria due to nontarget lymph nodes and frequently presents sclerotic bone metastases. Evaluation with BS is also remains a challenge to reliably prove therapy response due to frequently seen flare phenomenon. Despite efforts in standardization by Prostate Cancer Clinical Trials Working Group consensus recommendations[69] and European Organization for Research and Treatment[70] cancer imaging group, response assessment in metastatic PCa poses a significant challenge to clinicians in the clinical trials. Radiolabeled choline PET imaging has had promising results in predicting the response to treatment modalities, such as ADTs.[71] Early experience suggests that PSMA PET/CT may be more robust and reliable than choline PET/CT or conventional imaging but there are currently no data available to support its use, and research is required to validate this as a new biomarker (**Figs. 4** and **5**). Assessment of response by molecular imaging incorporating PSMA and other tracers, such as fluorodeoxyglucose (FDG), may potentially pave the way to address the heterogeneity of response to treatment in particular in the advanced stages of the PCa.

Interpretation and Pitfalls

Clinical studies so far convincingly demonstrate that 68Ga-PSMA is a promising tracer for both staging high-risk patients and detection of biochemical recurrence. The experience with 68Ga-PSMA PET/CT in clinical practice, however, continues to evolve and several pitfalls have become apparent.

Physiologic distribution of gallium-68 prostate-specific membrane antigen

Any focal uptake of 68Ga-PSMA higher than the surrounding background, in particular in the typical lymphatic drainage of the prostate, has to be considered malignant. To provide an accurate interpretation of 68Ga-PSMA, however, nuclear medicine specialists and radiologists should be familiar with physiologic PSMA distribution, common variants, artifacts, pattern of locoregional and distant spread of PCa, and its inherent pitfalls.

The physiologic PSMA uptake can be observed in the following tissues: lacrimal gland, parotid gland, submandibular gland, liver, spleen, small intestine, colon, and kidney (see **Fig. 1**). Depending on the type of PSMA used in the imaging, however, there is slight variability in the distribution of and intensity of uptake in these organs. Nonetheless, kidneys, urinary collecting system, and salivary glands are consistently demonstrating the highest radiotracer uptake.
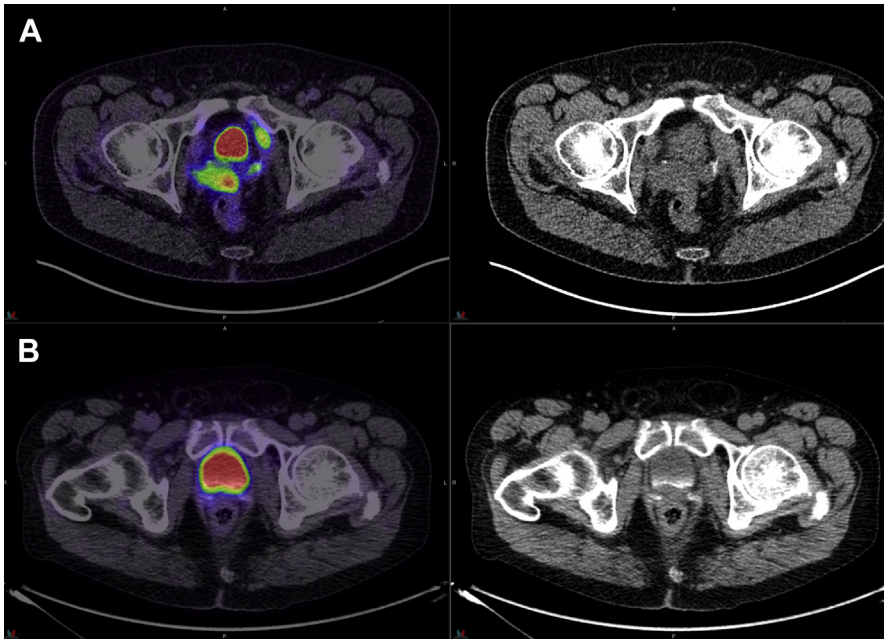
Fig. 4. Top row (*A*). PSMA PET/CT (*left*) and CT (*right*) images demonstrate intensely PSMA avid soft tissue in the prostatic fossa and left pelvis (not shown). Bottom row (*B*). PET/CT (*left*) and CT (*right*) show resolution of uptake and soft tissue lesion after chemotherapy consistent with complete response. Urinary activity is seen in the partially enhanced bladder.

Local recurrence and nodal metastases

The most common pattern of nodal spread in PCa is through pelvic and retroperitoneal nodes. Care should be taken, however, not to mistake a celiac ganglion with a small lymph node. It is known that celiac ganglia show a relevant ^{68}Ga-PSMA uptake. In a study by Krohn and colleagues,[72] at least 1 ganglion with tracer uptake was found in 76 of 85
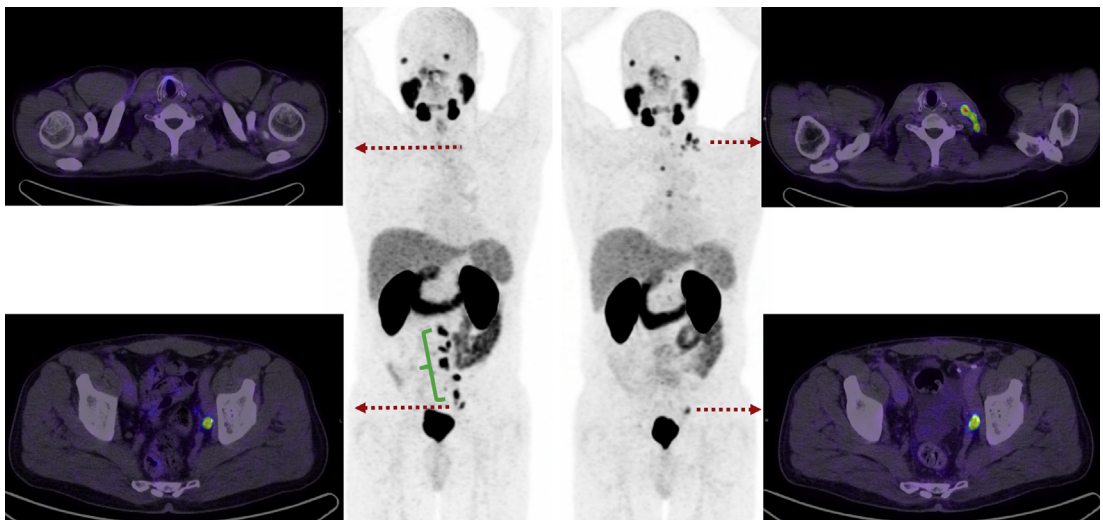

Fig. 5. (*Left*) A 68 year old with biochemical relapse with retroperitoneal nodal disease (*parenthesis*) on baseline PSMA PET MIP and corresponding PET/CT images of the pelvis (*dashed arrow, bottom left*) with no evidence of disease in the supraclavicular region (*dashed arrow, top left*). (*Right*) Four months after retroperitoneal nodal dissection with rising PSA from 1.4 ng/mL to 3.4 ng/mL in 1 month. PSMA PET MIP image shows resolution of retroperitoneal lymph nodes except one lymph node (*dashed arrow, bottom right*) and development of new nodal disease caudal to the surgical bed in the retroperitoneum, in the mediastinum and left supraclavicular region (*dashed arrow, top right*) as well as multiple osseous metastases.

patients (89.4%) undergoing 68Ga-PSMA PET/CT examination, which may mimic lymph node metastases in this area. Typical location of celiac ganglia at the level between the origins of the celiac and superior mesenteric arteries and symmetric uptake on both sides should assist in delineating these organs. Similarly, PSMA uptake in the colonic ganglia and stellate ganglia has been observed.[73]

Due to significant radiotracer excretion from kidneys and accumulation in ureters and the urinary bladder, small lymph nodes in the proximity of the ureters could potentially be obscured. Several approaches have been used to address this issue. Kabasakal and colleagues[74] performed early (at 5 minutes) and delayed (at 45–60 minutes) pelvic images. No difference was found in the number of lesions detected within the field of view. In early pelvic images, the assessment of the primary tumor and local lesions was easier because of lack of accumulated bladder activity. The intensity of uptake was significantly lower in early images, however, compared with late pelvic images. Rauscher and colleagues[75] described their departmental protocol where intravenous diuretic at the time of tracer injection is used to enhance the diuresis. This was used to improve image quality by reducing artifacts due to high activity of tracer in the bladder and the urinary

collection system. They have also suggested that this would be more relevant when PET/MR imaging is used by avoiding the commonly seen halo artifact around the areas of the urine collection.[40] In a retrospective study at the authors' institution, intravenous contrast media was administered and delayed time point CT in the urogram phase was acquired as part of PET/CT protocol. Of 50 patients who were imaged, CT urogram was helpful in final interpretation of 60% of the cases and in 50% of patients with high clinical impact by either delineating or excluding the solitary site of local or nodal recurrence[76] (**Fig. 6**). The authors propose this method as a 1-stop imaging procedure for 68Ga-PSMA without the need to perform multiple time-point imaging in particular in busy nuclear medicine departments.

Osseous metastases

BS provides a whole-body overview evaluating the presence of bone metastases. Preliminary data indicate, however, that the detection rate of 68Ga-PSMA PET/CT is clearly superior to the BS.[77] Pyka and colleagues,[78] in a study of 126 patients with PCa, have shown the higher diagnostic performance of 68Ga-PSMA PET compared with the BS. In this study, PSMA PET sensitivity and specificity of the overall bone involvement were 98.7% to 100% and 88.2% to 100% for PET
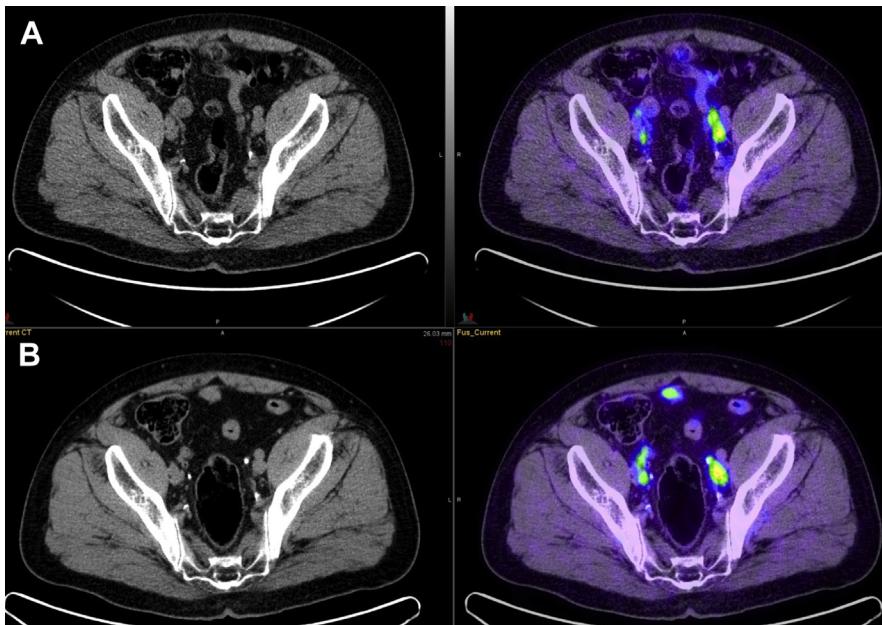

Fig. 6. Top row (*A*). PSMA PET/CT (*left*) and CT (*right*) in a patient with biochemical relapse of PCa demonstrates 2 foci of uptake in the left and one in the right side of pelvis. Bottom row (*B*). PSMA PET/CT urogram protocol (*left*) and CT urogram (*right*) in the same patient. Enhanced ureters/ureteric activity are easily differentiated from PSMA avid nodal disease.

compared with 86.7% to 89.3% and 60.8% to 96.1% for BS and of region-based analysis were 98.8% to 99.0% and 98.9% to 100% for PET compared with 82.4% to 86.6% and 91.6% to 97.9% for BS. The majority of these patients had only planar BS and only 30 patients underwent an additional single-photon emission CT. It seems, however, that BS in patients who have undergone PSMA PET only rarely offers additional information.[78]

Although moderate or intense focal uptake in bones usually indicate the presence of bone metastases, this should be interpreted in conjunction with findings on corresponding CT because PSMA uptake could be seen in other pathologies. In addition, faint uptake in various regions of the skeleton, especially in the ribs, can be found and, therefore, clinical caution needs to be taken because it remains unclear whether this uptake is really related to bone metastasis or might constitute false-positive findings. Artigas and colleagues[79] reported increased ^{68}Ga-PSMA uptake in a patient with Paget disease likely related to an overexpression of PSMA in areas with an abnormal bone remodeling and increased vascularity. In addition, healing fractures for example, ribs or pelvis, are known to potentially show faint increased PSMA ligand uptake.[80]

Visceral metastases

Visceral metastases are less common than lymph node or bone metastases and occur predominantly in the later course of disease[81] and have negative prognostic implications.[82] In a postmortem study, the predominant sites of visceral metastases in patient with distant metastases were lung (46%), liver (25%), pleura (21%), and adrenals (13%).[83] The differentiation between PCa metastases and lesions of different origin using conventional imaging may be challenging and, in many cases, warrants histologic clarification.

The differentiation between lung metastases for PCa and lesions of different origin, for example, primary lung cancer or even a non-neoplastic etiology, is a common clinical question. In study by Wang and colleagues,[84] immunohistochemistry analysis was performed to detect PSMA expression in a total of 150 lung specimens of patients with lung cancer. It was shown that PSMA is expressed not only in 85% of tumor neovasculature endothelial cells of non–small cell lung carcinomas (NSCLCs) and 70% of small cell lung carcinomas but also in 54% of tumor cells of NSCLC patients.[84] Pyka and colleagues[85] performed a study on lung lesions found on ^{68}Ga-PSMA PET/CT; 89 lesions in 45 patients were identified, 76 of which were classified as metastatic PCa (39 proved and 37 highly probable), 7 as primary lung cancer, and 2

as activated tuberculosis; 4 lesions remained unclear. On quantitative (standardized uptake value) analysis of ^{68}Ga-PSMA, PET was not able to discriminate between pulmonary metastases and primary lung cancer in PCa patients.[85] Therefore, morphologic characteristics of the lung lesions is of paramount importance in the interpretation of ^{68}Ga-PSMA PET because it is well known to be the case for FDG PET/CT studies (**Fig. 7**).

High background activity in the liver potentially can conceal liver metastases. In addition, in advanced disease, liver metastases especially tend to loose PSMA expression—most likely due to dedifferentiation. Therefore, in advanced disease, correlation with contrast-enhanced CT or MR imaging is required. Despite multimodality imaging, differentiation between PCa metastases and lesions of different origin, especially when PSMA negative, can be challenging and histologic clarification may be warranted.

Prostate-specific membrane antigen expression in other pathologies

Because ^{68}Ga-PSMA PET/CT imaging is a new imaging technique, it is important to be aware that ^{68}Ga-PSMA it is not completely specific for PCa to avoid scan misinterpretation. Intense staining for PSMA has been observed in endothelial cells of capillary vessels in peritumoral and endotumoral areas of some solid organ malignancies, which has been attributed to tumor angiogenesis. These tumors includes colon cancer, breast cancer, renal cell carcinoma, and transitional cell carcinoma. PSMA expression was also noted in subpopulation of neuroendocrine cells.[10] Other investigators have reported increased PSMA expression for other malignancies, such as glioblastoma, hepatocellular carcinoma, pancreatic cancer, and thyroid cancer.[85–89]

There have been increasing case reports of increased PSMA uptake in benign lesions, such as thyroid adenoma, Paget disease, schwannoma, tuberculosis, adrenal adenoma, and splenic sarcoidosis[90–92] (**Figs. 8** and **9**).

Finally, not all cases of PCa exhibit a significant PSMA overexpression. In a study of Maurer and colleagues,[93] approximately 8% of patients with primary PCa did not show PSMA overexpression—with currently no specific biological explanation.

Summary

Experience with ^{68}Ga-PSMA PET/CT has rapidly evolved since it was first described by the Heidelberg group in 2013. Although it was first used for detection of biochemical recurrence, it also has a role in staging high-risk patients prior to surgery
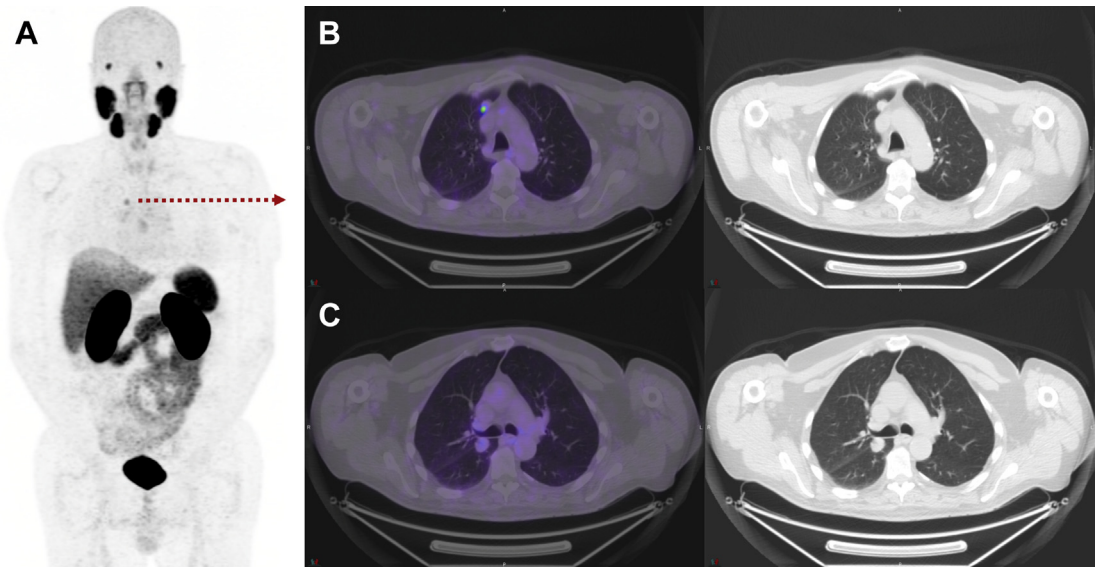
Fig. 7. PSMA PET MIP image (*A*) shows mild uptake in the lung (*dashed arrow*). Top row (*B*) PSMA PET/CT (*left*) and CT (*right*) images demonstrate low grade uptake in the lung metastases (histologically proved) from PCa. Bottom row (*C*). PET/CT (*left*) and CT (*right*) images show the other lung metastases with no increased PSMA uptake.

or radiotherapy and restaging patients with known metastases to assess response to systemic therapy. There is also an evolving role for using ^{68}Ga-PSMA PET/CT to select patients who may be suitable for ^{177}Lu-PSMA radionuclide therapy. Further research is needed to establish the indications where PSMA PET/CT may improve patient outcomes and whether it should be used in addition to or replace conventional imaging modalities (**Table 1**). Newer-generation PSMA ligands, including kit-based ^{68}Ga or ^{18}F
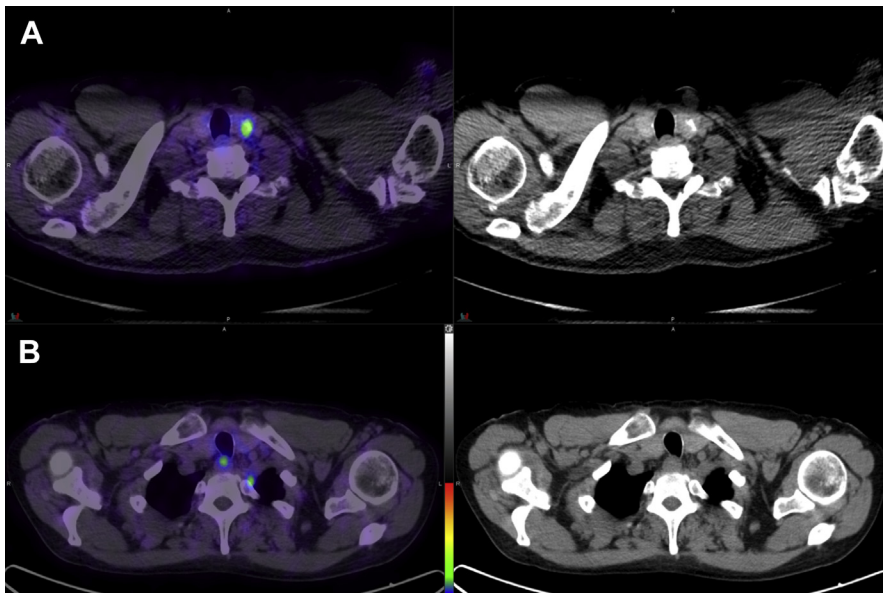

Fig. 8. Top row (*A*). PSMA PET/CT (*left*) and CT (*right*) images demonstrate focal activity corresponding to a partially calcified thyroid nodule. Bottom row (*B*). PSMA PET/CT (*left*) and CT (*right*) images show focal activity in the expected anatomic region of stellate ganglion.
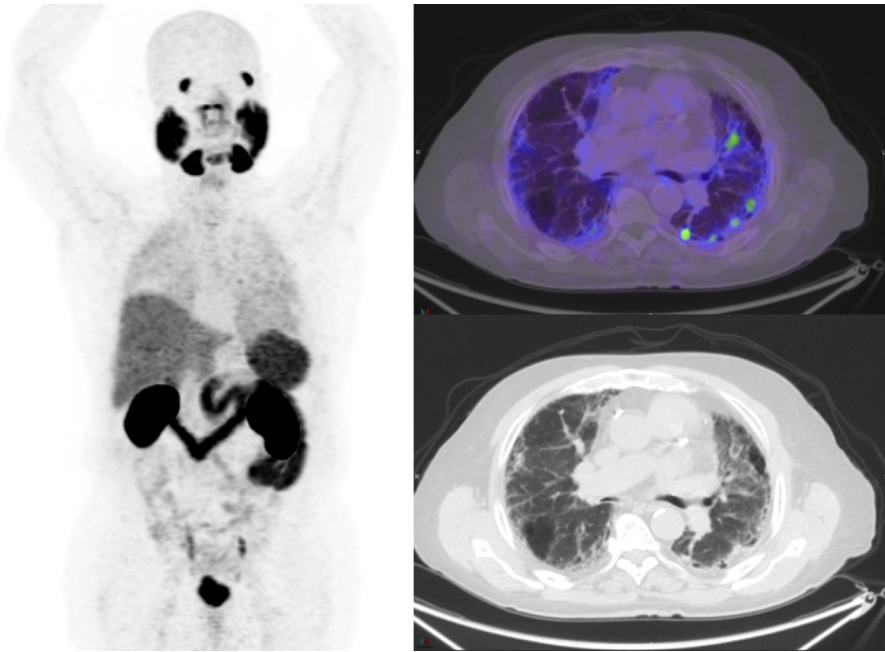
Fig. 9. PSMA PET of a 75-year-old man with biochemical relapse of PCa with PSA of 1.8 ng/L. MIP (*left*), PET/CT (*top right*) and CT (*bottom right*) images demonstrate diffuse uptake in the lungs consistent with the known history of interstitial lung disease.

Table 1
A summary of evolving clinical indications for prostate-specific membrane antigen PET/CT

Benefit Using ^{68}Ga-PSMA PET/CT	Patient Group
High clinical yield	• Primary staging in high-risk disease (D'Amico risk classification) • Biochemical recurrence with low PSA values (0.2 ng/mL to 10 ng/mL)
Low clinical yield	• Primary staging in low-risk and intermediate-risk disease (D'Amico risk classification)
Potential application with promising preliminary data	• Biopsy targeting after previous negative biopsy but high suspicion of PCa (especially in combination with multiparametric MR imaging using PET/MR imaging)
Potential application with current lack of published data	• Monitoring of systemic treatment in metastatic castration-resistant PCa • Monitoring of systemic treatment in metastatic castration-sensitive PCa • Active surveillance of the primary (especially in combination with multiparametric MR imaging using PET/MR imaging) • Active surveillance of the low-volume indolent metastatic PCa • Treatment monitoring in metastatic castration-resistant PCa undergoing radioligand therapy targeting PSMA (eg, ^{177}Lu-PSMA ligand)

Adapted from Rauscher I, Maurer T, Fendler WP, et al. (68)Ga-PSMA ligand PET/CT in patients with prostate cancer: how we review and report. Cancer Imaging 2016;16(1):14.

derivatives, may further improve accuracy and availability.

REFERENCES

1. Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol 2008;63(4):387–95.
2. Jadvar H. Molecular imaging of prostate cancer with PET. J Nucl Med 2013;54(10):1685–8.
3. Afshar-Oromieh A, Haberkorn U, Hadaschik B, et al. PET/MRI with a 68Ga-PSMA ligand for the detection of prostate cancer. Eur J Nucl Med Mol Imaging 2013;40(10):1629–30.
4. Afshar-Oromieh A, Malcher A, Eder M, 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(4):486–95.
5. Roethke MC, Kuru TH, Afshar-Oromieh A, et al. Hybrid positron emission tomography-magnetic resonance imaging with gallium 68 prostate-specific membrane antigen tracer: a next step for imaging of recurrent prostate cancer-preliminary results. Eur Urol 2013;64(5):862–4.
6. Israeli RS, Powell CT, Fair WR, et al. Molecular cloning of a complementary DNA encoding a prostate-specific membrane antigen. Cancer Res 1993;53(2):227–30.
7. Mease RC, Foss CA, Pomper MG. PET imaging in prostate cancer: focus on prostate-specific membrane antigen. Curr Top Med Chem 2013;13(8):951–62.
8. Demirkol MO, Acar Ö, Uçar B, et al. Prostate-specific membrane antigen-based imaging in prostate cancer: impact on clinical decision making process. Prostate 2015;75(7):748–57.
9. Sokoloff RL, Norton KC, Gasior CL, et al. A dual-monoclonal sandwich assay for prostate-specific membrane antigen: levels in tissues, seminal fluid and urine. Prostate 2000;43(2):150–7.
10. Silver DA, Pellicer I, Fair WR, et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res 1997;3(1):81–5.
11. Bouchelouche K, Choyke PL, Capala J. Prostate specific membrane antigen- a target for imaging and therapy with radionuclides. Discov Med 2010;9(44):55–61.
12. Conway RE, Petrovic N, Li Z, et al. Prostate-specific membrane antigen regulates angiogenesis by modulating integrin signal transduction. Mol Cell Biol 2006;26(14):5310–24.
13. Ananias HJ, van den Heuvel MC, Helfrich W, et al. Expression of the gastrin-releasing peptide receptor, the prostate stem cell antigen and the prostate-specific membrane antigen in lymph node and bone metastases of prostate cancer. Prostate 2009;69(10):1101–8.
14. Minner S, van den Heuvel MC, Helfrich W, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. Prostate 2011;71(3):281–8.
15. Rybalov M, Ananias HJ, Hoving HD, et al. PSMA, EpCAM, VEGF and GRPR as imaging targets in locally recurrent prostate cancer after radiotherapy. Int J Mol Sci 2014;15(4):6046–61.
16. Bostwick DG, Pacelli A, Blute M, et al. Prostate specific membrane antigen expression in prostatic intra-epithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer 1998;82(11):2256–61.
17. Graham K, Lesche R, Gromov AV, et al. Radiofluorinated derivatives of 2-(phosphonomethyl)pentanedioic acid as inhibitors of prostate specific membrane antigen (PSMA) for the imaging of prostate cancer. J Med Chem 2012;55(22):9510–20.
18. Kawakami M, Nakayama J. Enhanced expression of prostate-specific membrane antigen gene in prostate cancer as revealed by in situ hybridization. Cancer Res 1997;57(12):2321–4.
19. Troyer JK, Beckett ML, Wright GL Jr. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids. Int J Cancer 1995;62(5):552–8.
20. Wright GL Jr, Grob BM, Haley C, et al. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. Urology 1996;48(2):326–34.
21. Ross JS, Sheehan CE, Fisher HA, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res 2003;9(17):6357–62.
22. Horoszewicz JS, Kawinski E, Murphy GP. Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients. Anticancer Res 1987;7(5B):927–35.
23. Franc BL, Cho SY, Rosenthal SA, et al. Detection and localization of carcinoma within the prostate using high resolution transrectal gamma imaging (TRGI) of monoclonal antibody directed at prostate specific membrane antigen (PSMA)–proof of concept and initial imaging results. Eur J Radiol 2013;82(11):1877–84.
24. Ponsky LE, Cherullo EE, Starkey R, et al. Evaluation of preoperative ProstaScint scans in the prediction of nodal disease. Prostate Cancer Prostatic Dis 2002;5(2):132–5.
25. Liu H, Rajasekaran AK, Moy P, et al. Constitutive and antibody-induced internalization of prostate-specific membrane antigen. Cancer Res 1998;58(18):4055–60.
26. Bander NH, Trabulsi EJ, Kostakoglu L, et al. Targeting metastatic prostate cancer with radiolabeled monoclonal antibody J591 to the extracellular

domain of prostate specific membrane antigen. J Urol 2003;170(5):1717–21.

27. Tagawa ST, Milowsky MI, Morris M, et al. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res 2013;19(18):5182–91.

28. Tsukamoto T, Wozniak KM, Slusher BS. Progress in the discovery and development of glutamate carboxypeptidase II inhibitors. Drug Discov Today 2007;12(17–18):767–76.

29. Foss CA, Mease RC, Fan H, et al. Radiolabeled small-molecule ligands for prostate-specific membrane antigen: in vivo imaging in experimental models of prostate cancer. Clin Cancer Res 2005; 11(11):4022–8.

30. Mease RC, Dusich CL, Foss CA, et al. N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: a new imaging probe for prostate cancer. Clin Cancer Res 2008;14(10): 3036–43.

31. Maresca KP, Hillier SM, Femia FJ, et al. A series of halogenated heterodimeric inhibitors of prostate specific membrane antigen (PSMA) as radiolabeled probes for targeting prostate cancer. J Med Chem 2009;52(2):347–57.

32. Banerjee SR, Foss CA, Castanares M, et al. Synthesis and evaluation of technetium-99m- and rhenium-labeled inhibitors of the prostate-specific membrane antigen (PSMA). J Med Chem 2008;51(15):4504–17.

33. Hillier SM, Maresca KP, Lu G, et al. 99mTc-labeled small-molecule inhibitors of prostate-specific membrane antigen for molecular imaging of prostate cancer. J Nucl Med 2013;54(8):1369–76.

34. Banerjee SR, Pullambhatla M, Byun Y, et al. 68Ga-labeled inhibitors of prostate-specific membrane antigen (PSMA) for imaging prostate cancer. J Med Chem 2010;53(14):5333–41.

35. Schafer M, Bauder-Wüst U, Leotta K, et al. A dimerized urea-based inhibitor of the prostate-specific membrane antigen for 68Ga-PET imaging of prostate cancer. EJNMMI Res 2012;2(1):23.

36. Chen Y, Pullambhatla M, Banerjee SR, et al. Synthesis and biological evaluation of low molecular weight fluorescent imaging agents for the prostate-specific membrane antigen. Bioconjug Chem 2012;23(12):2377–85.

37. Barrett JA, Coleman RE, Goldsmith SJ, et al. First-in-man evaluation of 2 high-affinity PSMA-avid small molecules for imaging prostate cancer. J Nucl Med 2013;54(3):380–7.

38. Vallabhajosula S, Nikolopoulou A, Babich JW, et al. 99mTc-labeled small-molecule inhibitors of prostate-specific membrane antigen: pharmacokinetics and biodistribution studies in healthy subjects and patients with metastatic prostate cancer. J Nucl Med 2014;55(11):1791–8.

39. Cho SY, Gage KL, Mease RC, et al. Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. J Nucl Med 2012;53(12):1883–91.

40. Afshar-Oromieh A, Haberkorn U, Schlemmer HP, et al. Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience. Eur J Nucl Med Mol Imaging 2014; 41(5):887–97.

41. Afshar-Oromieh A, Zechmann CM, Malcher A, 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(1):11–20.

42. Zechmann CM, Afshar-Oromieh A, Armor T, 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(7):1280–92.

43. Reubi JC, Maecke HR. Peptide-based probes for cancer imaging. J Nucl Med 2008;49(11):1735–8.

44. Hofman MS, Kong G, Neels OC, et al. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. J Med Imaging Radiat Oncol 2012;56(1):40–7.

45. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics 2015;35(2):500–16.

46. Eder M, Schäfer M, Bauder-Wüst U, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem 2012;23(4):688–97.

47. Roesch F, Riss PJ. The renaissance of the (6)(8)Ge/(6)(8)Ga radionuclide generator initiates new developments in (6)(8)Ga radiopharmaceutical chemistry. Curr Top Med Chem 2010;10(16):1633–68.

48. Afshar-Oromieh A, Hetzheim H, Kübler W, 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(9):1611–20.

49. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65(2):467–79.

50. Jereczek-Fossa BA, Beltramo G, Fariselli L, et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys 2012;82(2):889–97.

51. Afshar-Oromieh A, Avtzi E, Giesel FL, 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(2):197–209.

52. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid (6)(8)Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 2015;56(5):668–74.

53. Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive 68Ga-Prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70(6):926–37.

54. Brogsitter C, Zophel K, Kotzerke J. 18F-Choline, 11C-choline and 11C-acetate PET/CT: comparative analysis for imaging prostate cancer patients. Eur J Nucl Med Mol Imaging 2013;40(Suppl 1):S18–27.

55. Bluemel C, Krebs M, Polat B, et al. 68Ga-PSMA-PET/CT in patients with biochemical prostate cancer recurrence and negative 18F-choline-PET/CT. Clin Nucl Med 2016;41(7):515–21.

56. Rauscher I, Maurer T, Beer AJ, et al. Value of 68Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. J Nucl Med 2016;57(11):1713–9.

57. Giesel FL, Fiedler H, Stefanova M, et al. PSMA PET/CT with Glu-urea-Lys-(Ahx)-[(6)(8)Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42(12):1794–800.

58. Ceci F, Uprimny C, Nilica B, 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(8):1284–94.

59. Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol 2009; 55(6):1251–65.

60. Eiber M, Maurer T, Beer AJ, et al. Prospective evaluation of PSMA-PET imaging for preoperative lymph node staging in prostate cancer. J Nucl Med 2014; 55(Suppl 1):20.

61. Budaus L, Leyh-Bannurah SR, Steuber T, et al. Initial experience of (68)Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. Eur Urol 2016;69(3):393–6.

62. Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014;65(4):809–15.

63. Wu LM, Xu JR, Ye YQ, et al. The clinical value of diffusion-weighted imaging in combination with T2-weighted imaging in diagnosing prostate carcinoma: a systematic review and meta-analysis. AJR Am J Roentgenol 2012;199(1):103–10.

64. Muller BG, Shih JH, Sankineni S, et al. Prostate cancer: interobserver agreement and accuracy with the revised prostate imaging reporting and data system at multiparametric MR imaging. Radiology 2015; 277(3):741–50.

65. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65(1):124–37.

66. Maurer T, Beer AJ, Wester HJ, et al. Positron emission tomography/magnetic resonance imaging with 68Gallium-labeled ligand of prostate-specific membrane antigen: promising novel option in prostate cancer imaging? Int J Urol 2014;21(12):1286–8.

67. Fendler WP, Schmidt DF, Wenter V, et al. 68Ga-PSMA-HBED-CC PET/CT detects location and extent of primary prostate cancer. J Nucl Med 2016;57(11):1720–5.

68. Mowatt G, Scotland G, Boachie C, et al. The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation. Health Technol Assess 2013;17(20):vii–xix, 1–281.

69. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26(7):1148–59.

70. Lecouvet FE, Talbot JN, Messiou C, et al. Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: a review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer 2014;50(15): 2519–31.

71. De Giorgi U, Caroli P, Scarpi E, et al. (18)F-Fluorocholine PET/CT for early response assessment in patients with metastatic castration-resistant prostate cancer treated with enzalutamide. Eur J Nucl Med Mol Imaging 2015;42(8):1276–83.

72. Krohn T, Verburg FA, Pufe T, et al. [(68)Ga]PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. Eur J Nucl Med Mol Imaging 2015;42(2):210–4.

73. Chang SS, Reuter VE, Heston WD, et al. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res 1999;59(13):3192–8.

74. Kabasakal L, Demirci E, Ocak M, et al. Evaluation of PSMA PET/CT imaging using a 68Ga-HBED-CC ligand in patients with prostate cancer and the value of early pelvic imaging. Nucl Med Commun 2015; 36(6):582–7.

75. Rauscher I, Maurer T, Fendler WP, et al. (68)Ga-PSMA ligand PET/CT in patients with prostate cancer: How we review and report. Cancer Imaging 2016;16(1):14.

76. Iravani A, Mulcahy T, Hofman M, et al. The diagnostic value of 68Ga PSMA-HBED PET with CT urogram protocol in the initial staging and biochemical relapse of prostate cancer. Intern Med J 2016;46(Suppl 1):6.

77. Eiber M, Pyka T, Okamoto S, et al. 68Gallium-HBED-CC-PSMA PET compared to conventional bone scintigraphy for evaluation of bone metastases in prostate cancer patients. European Urology Supplements 2016;15(3):e566.

78. Pyka T, Okamoto S, Dahlbender M, et al. Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. Eur J Nucl Med Mol Imaging 2016;43(12):2114–21.

79. Artigas C, Alexiou J, Garcia C, et al. Paget bone disease demonstrated on (68)Ga-PSMA ligand PET/CT. Eur J Nucl Med Mol Imaging 2016;43(1):195–6.

80. Gykiere P, Goethals L, Everaert H. Healing sacral fracture masquerading as metastatic bone disease on a 68Ga-PSMA PET/CT. Clin Nucl Med 2016; 41(7):e346–7.

81. Moschini M, Sharma V, Zattoni F, et al. Natural history of clinical recurrence patterns of lymph node-positive prostate cancer after radical prostatectomy. Eur Urol 2016;69(1):135–42.

82. Goodman OB Jr, Flaig TW, Molina A, et al. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 2014;17(1):34–9.

83. Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 2000;31(5):578–83.

84. Wang HL, Wang SS, Song WH, et al. Expression of prostate-specific membrane antigen in lung cancer cells and tumor neovasculature endothelial cells and its clinical significance. PLoS One 2015;10(5): e0125924.

85. Pyka T, Weirich G, Einspieler I, et al. 68Ga-PSMA-HBED-CC PET for differential diagnosis of suggestive lung lesions in patients with prostate cancer. J Nucl Med 2016;57(3):367–71.

86. Rowe SP, Gorin MA, Hammers HJ, et al. Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted (1)(8)F-DCFPyL PET/CT. Ann Nucl Med 2015;29(10):877–82.

87. Sasikumar A, Joy A, Nanabala R, et al. (68)Ga-PSMA PET/CT imaging in primary hepatocellular carcinoma. Eur J Nucl Med Mol Imaging 2016; 43(4):795–6.

88. Schwenck J, Tabatabai G, Skardelly M, et al. In vivo visualization of prostate-specific membrane antigen in glioblastoma. Eur J Nucl Med Mol Imaging 2015; 42(1):170–1.

89. Verburg FA, Krohn T, Heinzel A, et al. First evidence of PSMA expression in differentiated thyroid cancer using [(6)(8)Ga]PSMA-HBED-CC PET/CT. Eur J Nucl Med Mol Imaging 2015;42(10):1622–3.

90. Kanthan GL, Drummond J, Schembri GP, et al. Follicular thyroid adenoma showing avid uptake on 68Ga PSMA-HBED-CC PET/CT. Clin Nucl Med 2016;41(4):331–2.

91. Kobe C, Maintz D, Fischer T, et al. Prostate-specific membrane antigen PET/CT in splenic sarcoidosis. Clin Nucl Med 2015;40(11):897–8.

92. Rischpler C, Maurer T, Schwaiger M, et al. 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(1):193–4.

93. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic efficacy of (68)Gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol 2016;195(5):1436–43.