

Current use of PSMA–PET in prostate cancer management

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Abstract | Currently, the findings of imaging procedures used for detection or staging of prostate cancer depend on morphology of lymph nodes or bone metabolism and do not always meet diagnostic needs. Prostate-specific membrane antigen (PSMA), a transmembrane protein that has considerable overexpression on most prostate cancer cells, has gained increasing interest as a target molecule for imaging. To date, several small compounds for labelling PSMA have been developed and are currently being investigated as imaging probes for PET with the ⁶⁸Ga-labelled PSMA inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC being the most widely studied agent.

⁶⁸Ga-PSMA–PET imaging in combination with multiparametric MRI (mpMRI) might provide additional molecular information on cancer localization within the prostate. In patients with primary prostate cancer of intermediate-risk to high-risk, PSMA-based imaging has been reported to improve detection of metastatic disease compared with CT or mpMRI, rendering additional cross-sectional imaging or bone scintigraphy unnecessary. Furthermore, in patients with biochemically recurrent prostate cancer, use of ⁶⁸Ga-PSMA–PET imaging has been shown to increase detection of metastatic sites, even at low serum PSA values, compared with conventional imaging or PET examination with different tracers. Thus, although current knowledge is still limited and derived mostly from retrospective series, PSMA-based imaging holds great promise to improve prostate cancer management.

With an estimated incidence of 1,111,700 cases per year and an estimated mortality of 307,000 men per year, prostate cancer is one of the most prevalent cancers worldwide¹. In western countries prostate cancer is the most common cancer in men, with roughly 758,700 new cases diagnosed per year, and it is the third most common cause of cancer-associated mortality in men¹. Thus, accurate diagnosis and staging of prostate cancer is of upmost importance.

According to current guidelines, diagnosis of prostate cancer is most commonly made by sonography-guided needle biopsy^{2,3}. In men in whom prostate cancer is suspected but histological findings are negative, MRI has evolved as the standard imaging procedure^{3,4}. Suspicious lesions on MRI facilitate histological confirmation of prostate cancer by aiding targeted sampling in subsequent biopsies^{5,6}. However, a certain portion of prostate cancer lesions might still be missed using MRI^{7–10}. In these patients, additional molecular information obtained by PET imaging with prostate-cancer-specific tracers is desirable.

After diagnosis, patients with histologically confirmed prostate cancer are stratified to distinct risk groups according to their digital-rectal examination

results, the level of serum PSA and histological findings following analysis of the biopsy sample^{3,11}. In patients with intermediate-risk to high-risk prostate cancer, CT or MRI of the lower abdomen accompanied by bone scintigraphy are currently recommended in guidelines from the European Association of Urology³ and the National Comprehensive Cancer Network¹¹. In patients with recurrent and/or metastatic prostate cancer, bone scintigraphy, CT and MRI are recommended for detecting tumours or evaluating treatment responses^{3,11}. Newer imaging modalities that have been investigated for use in prostate cancer diagnosis and staging include PET with choline-based tracers or fluorodeoxyglucose^{12,13}; however, despite these advances in imaging, these procedures still have considerable limitations and are not always able to meet diagnostic needs as they do not always reliably identify local recurrence, lymph node involvement or visceral metastases^{3,13–19}.

The use of PET probes targeting prostate-specific membrane antigen (PSMA, also known as glutamate carboxypeptidase 2) for imaging prostate cancer has gained increasing interest and shows great promise for improving the management of patients with prostate cancer²⁰. This Review will provide an overview of

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doi:10.1038/nrurol.2016.26
Published online 23 Feb 2016

Key points

- Prostate-specific membrane antigen (PSMA) is a promising and specific target for prostate cancer imaging
- PSMA–PET imaging can add molecular information to multiparametric MRI and, therefore, delineate suspicious lesions for targeted biopsies, especially in patients whose biopsy samples are tumour-negative
- PSMA–PET imaging shows increased specificity and sensitivity compared with current standard imaging (CT, MRI and bone scintigraphy) in patients with primary intermediate-risk or high-risk prostate cancer
- PSMA–PET imaging improves detection of metastatic lesions even at low serum PSA values in biochemically recurrent prostate cancer
- Enhanced detection of prostate cancer lesions might enable improved patient-tailored therapy planning and, therefore, lead to improved therapy outcomes

current knowledge regarding PSMA targeting and imaging with PSMA ligands, and will highlight the possible clinical application of PSMA-based imaging to the management of patients with prostate cancer.

PSMA as a target in prostate cancer

PSMA is a type II transmembrane protein (FIG. 1), which has a 19-amino-acid intracellular portion, a 24-amino-acid transmembrane portion and a 707-amino-acid extracellular portion²¹. The *PSMA* gene (also known as *FOLH1*) is located on the short arm of chromosome 11 in a region that is not commonly deleted in patients with prostate cancer²². PSMA expression and localization in the normal human prostate is associated with the cytoplasm and apical side of the epithelium surrounding prostatic ducts but not basal epithelium, neuroendocrine or stromal cells²³. Cytoplasmic PSMA is truncated at the N-terminus and is called PSM', it has no folate-hydrolase activity or capacity to hydrolyse *N*-acetylserine/glutamic acid^{24,25}, and its function is not known. Dysplastic and/or neoplastic transformation of prostate tissue results in the transfer of PSMA from the apical membrane to the luminal surface of the ducts^{26,27}. The transition to androgen-independent prostate cancer eventually leads to further PSMA expression^{28,29}. The PSMA:PSM' ratio increases as prostate tumour cells increase in Gleason grade²⁶. Interestingly, PSMA expression has also been reported in the tumour neovasculature of some solid tumours (including colon, breast and renal cancer and subtypes of bladder cancer) and in newly formed blood vessels^{30–35}. PSMA is also expressed on astrocytes of the central nervous system and it is known as glutamate carboxypeptidase 2 in these cells^{36,37}.

Consequently, this nonprostatic PSMA expression has led to anecdotal reports of high uptake of PSMA inhibitors in a variety of lesions that are incidentally present in patients that have undergone PSMA–PET for staging or restaging of prostate cancer^{38–43}. PSMA is only enzymatically active in its homodimeric form⁴⁴, and is made up of two monomers with intracellular, transmembrane and extracellular domains⁴⁵. After a ligand (such as a small-molecule antagonist or a specific antibody) binds to PSMA, internalization occurs and it is either retained in lysosomal compartments, or released into the cytoplasm^{44,46}. PSMA is an ideal target for molecular imaging

of prostate cancer owing to its biological characteristics, including: considerable (100-fold to 1,000-fold) over-expression on the cell membrane of nearly all prostatic cancer cells compared with normal nontarget expression (on normal prostate epithelial cells, in the small intestine, renal tubular cells and the salivary glands)^{35,47–50}, increased expression in advanced-stage and castration-resistant prostate cancers — several studies exist showing that PSMA expression levels increase according to the stage and grade of the tumour^{35,47,51} — potentially enabling PSMA imaging to be used for prognosis, a large extracellular domain enabling targeting using antibodies and a cytoplasmic domain containing an internalization motif that results in internalization and endosomal recycling, which increases the deposition of conjugated radiometals into the cell with subsequent improvement of both imaging and therapeutic efficacy^{52,53}. This latter feature makes PSMA an attractive target, especially for developing small-molecule radiopharmaceuticals (PSMA inhibitors) that are typically cleared quickly from the bloodstream and have low background activity⁵⁴. However, the degree of internalization has not been fully investigated for all available PSMA inhibitors.

Since the 1980s, efforts have been made to target specific regions of the intracellular or extracellular domain of PSMA with monoclonal antibodies labelled with different isotopes for nuclear medicine imaging⁵⁵ (FIG. 1). To date, only one radiolabelled anti-PSMA antibody (ProstaScint[®], Jazz Pharmaceuticals, USA) targeting an intracellular epitope (7E11) of PSMA has been approved by the FDA⁵⁶. J591, a monoclonal antibody targeting the extracellular domain of PSMA, localizes to viable tumour cells and has shown effective image contrast in clinical trials⁵⁷. However, in general, the effectiveness of antibodies as diagnostic radiopharmaceuticals is limited by a long circulating half-life resulting in a high unspecific background activity and poor tumour penetrability. The combination of antibodies with long-lived PET radioisotopes (such as ⁸⁹Zr) or using only single-chain fragments (such as antibody fragments D7-Fc and D7-CH3) could be potential solutions to these limitations^{58–60}.

PSMA ligands

The identification of the active substrate recognition site of PSMA with its structural and functional homology to glutamate carboxypeptidase 2 (also known as *N*-acetylated- α -linked acidic dipeptidase I) promoted the development of small molecules as PSMA ligands or inhibitors^{61,62}. The recognition site contains two zinc ions and is composed of two pockets, the glutamate-sensing pocket (the S1' pocket) and the non-pharmacophore pocket (the S1 pocket). Most of the inhibitors have a zinc-binding component and glutamate or glutamate isostere, which resides in the S1' pocket⁶³. PSMA inhibitors fall into three families: phosphorous-based (including phosphonate, phosphate, and phosphoramidate), thiol-based and urea-based. Urea-based inhibitors have a high affinity for PSMA, specificity for PSMA and fast and efficient internalization in LNCaP cells⁵⁴; therefore, current research into small-molecule PSMA inhibitors is mainly focused on

these pharmaceutically engineered agents. The structural and functional variety of PSMA ligands and their development is reviewed elsewhere⁶⁴.

Several research groups have reported the use of small-molecule inhibitors of PSMA labelled with ¹²³I (REFS 65–67), ^{99m}Tc (REFS 68,69), ¹⁸F (REFS 70,71), ¹¹¹In (REFS 50,72) and ⁶⁸Ga (REFS 20,54,73–76).

The inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (⁶⁸Ga-PSMA-HBED-CC), which was initially described by Eder *et al.*⁵⁴ in 2012, is the most widely used agent for PET imaging. On binding to prostate cancer cells, internalization occurs and high accumulation of ⁶⁸Ga-PSMA-HBED-CC, even in small metastases, is observed. This agent is also rapidly cleared from nontarget tissue. Physiologically, this radiotracer shows enhanced accumulation in salivary glands, the liver, the spleen, the small bowel and the urinary tract⁷⁷. However, hardly any uptake is observed in retroperitoneal fatty tissue, benign lymphatic tissue and bone, which are locations where prostate cancer is likely to metastasize^{35,41,77}. ⁶⁸Ga-PSMA-HBED-CC has become a valuable diagnostic agent in monitoring of both recurrent prostate cancer and responses to therapy. N,N'-bis[2-hydroxy-5-(carboxyethyl)-benzyl]ethylenediamine-N,N'-diacetic acid (HBED-CC) can easily be labelled with ⁶⁸Ga at room temperature as it is an efficient ⁶⁸Ga chelator with fast complexing kinetics and good stability⁷⁸. Eder and colleagues⁵⁴ described its synthesis using HBED-CC, which is an analogue of hydroxybenzyl ethylenediamine (HBED). HBED is an attractive chelator for ⁶⁸Ga as they form a thermodynamically stable complex⁷⁴. In an initial preclinical *in vivo* study, PSMA-positive LNCaP tumour xenografts were visible at 1 h after injection and tumour:muscle and tumour:blood uptake ratios were favourable⁵⁴. Reports on the clinical value of ⁶⁸Ga-PSMA-HBED-CC in PET imaging of recurrent and primary prostate cancer showed that it has high detection rates compared with data from literature and in direct comparison with ¹⁸F-choline^{20,67–69,75–79}.

In 2015, a different ⁶⁸Ga-labelled PSMA ligand for PET imaging, EuK-Subkff-⁶⁸Ga-DOTAGA (⁶⁸Ga-PSMA Imaging & Therapy (I&T)) was introduced, which can also be labelled with ¹⁷⁷Lu or ¹¹¹In (REFS 50,76,79–81). Thus, it can serve as a theranostic agent for both imaging (⁶⁸Ga) and radioguided surgery (¹¹¹In) or PSMA-targeted endoradiotherapy (¹⁷⁷Lu). Another theranostic agent, referred to as PSMA-DKFZ-617, was described initially by Benešová and colleagues⁸², with the first studies using a ⁶⁸Ga-labelled compound and reporting low radiation exposure and very high contrast when used for detection of prostate cancer lesions^{82,83}. Currently, this agent is being investigated for use in PSMA-targeted endoradiotherapy^{84,85}.

The development of ¹⁸F-labelled PSMA compounds offers potential advances with regard to increasing the number of examinations possible, owing to a higher available amount of the radioisotope ¹⁸F produced by a cyclotron compared with ⁶⁸Ga eluted from a generator⁸⁶. An excellent image quality is also likely, which will result from optimized tracer doses leading to high imaging statistics and the decay properties of ¹⁸F itself

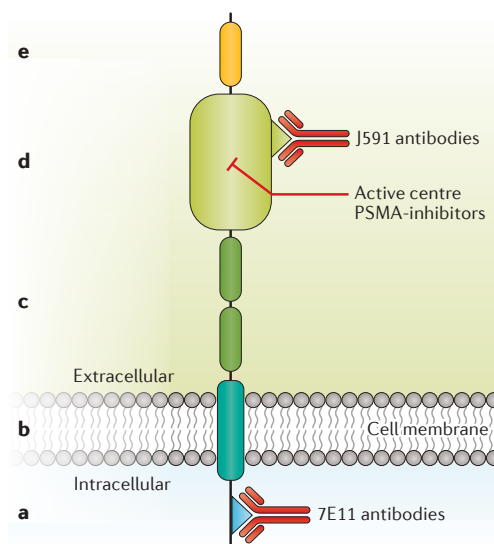


Figure 1 | The structure of prostate-specific membrane antigen (PSMA), its binding sites for PSMA ligands and the most frequently used antibodies. a | The short intracellular domain containing a binding site that can be targeted with 7E11 antibodies. **b |** The hydrophobic transmembrane region. The extracellular part of PSMA consists of section **c |** that contains two domains of unknown function and proline-rich and glycine-rich regions as linkers, **d |** that is the large catalytic domain, which contains a binding site for J591 antibodies as well as the active substrate recognition site that is being targeting by PSMA inhibitors and **e |** the final domain of unknown function to which a helical dimerization domain is localized.

(as it requires a much shorter distance to decelerate the positron in human tissue in comparison with ⁶⁸Ga owing to its low positron emission energy, resulting in higher image resolution)⁸⁶. Labelling PSMA with ¹⁸F could also be achieved by fluorinating the HBED compound. Malik and colleagues⁸⁷ showed this approach to be successful when they applied this agent to PSMA-positive LNCaP cells; however, further preclinical and clinical studies on the effectiveness of this agent are currently lacking.

Besides fluorination of known compounds, new, specifically ¹⁸F-labelled compounds have been reported. A first generation ¹⁸F-labelled PSMA ligand, ¹⁸F-DCFBC, was described by Mease and colleagues⁸⁸. PSMA-positive PC-3 PIP xenografts were clearly visible as early as 20–30 min after injection with only faint uptake observed in the PSMA-negative PC-3 FLU xenografts. In a clinical study, researchers investigated ¹⁸F-DCFBC in five patients who had radiological evidence of metastatic disease, and imaging with ¹⁸F-DCFBC identified more suspicious lesions than bone scintigraphy or CT, but whether any of these lesions were false positives was not investigated⁸⁹. In another preliminary study in 13 patients with primary prostate cancer, ¹⁸F-DCFBC–PET was able to reliably detect clinically significant high-grade and large-volume tumours (Gleason scores 8 and 9) with relatively low uptake in benign prostatic lesions⁷¹. The disadvantage of using this

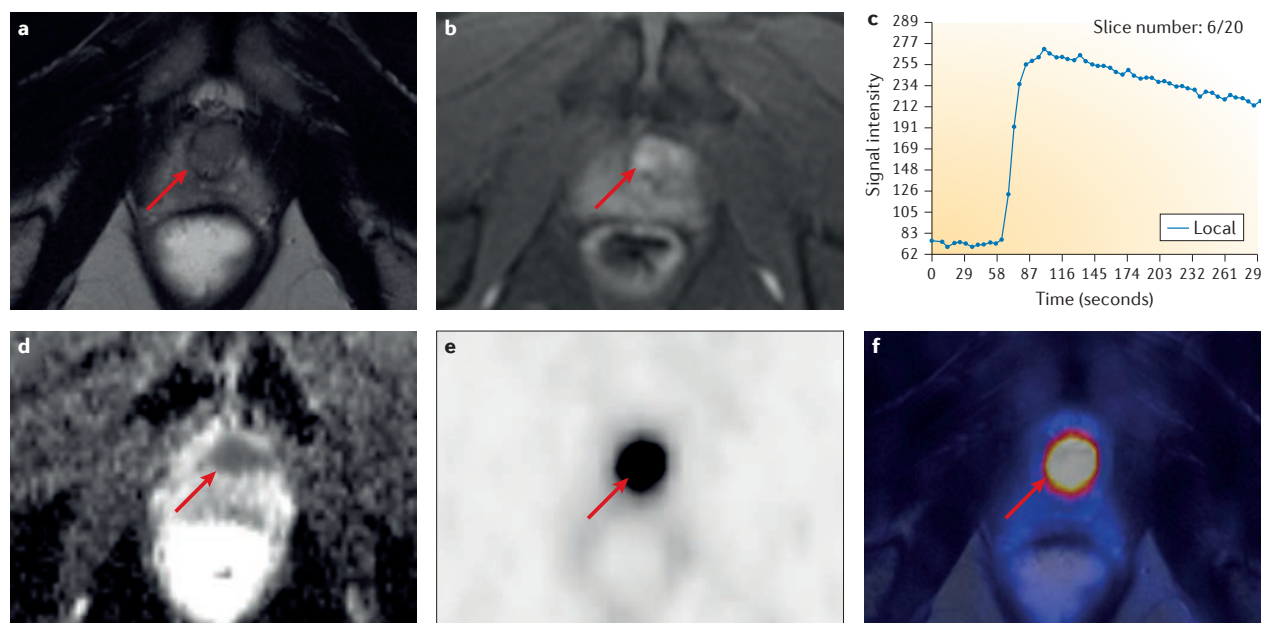


Figure 2 | ^{68}Ga -PSMA-PET-MRI of a 50-year-old patient who had a rising serum PSA value (16 ng/ml at imaging) and two tumour-negative previous biopsy samples. a | T2-weighted image showing a hypointense mass in the anterior fibromuscular stroma with pronounced arterial enhancement. b | Typical pronounced arterial contrast enhancement compared with the surrounding tissue. c | Intensity curve of the dynamic contrast enhanced sequence shows a typical fast washin followed by washout in the late phase. d | Diffusion-weighted imaging demonstrates markedly restricted diffusion. e | PET image and f | fused PET-MRI showing intense prostate-specific membrane antigen (PSMA) expression in the corresponding region. Targeted PET-MRI fusion biopsy revealed prostate cancer with Gleason score 7 in this region.

agent lies in the considerable activity of this agent in the bloodstream, which could potentially interfere with the detection of lymph-node metastases⁸⁹.

In 2011, a second generation ^{18}F -labelled PSMA ligand ^{18}F -DCFPyL was introduced, with favourable results for tissue binding *in vitro* and *in vivo*. High tumour uptake ratios between PSMA-positive PC3 PIP and PSMA-negative PC3 FLU xenografts were also observed⁷⁰. In the first clinical investigation in nine patients, ^{18}F -DCFPyL showed very high levels of uptake in sites of putative metastatic disease, as well as in primary tumours⁹⁰. Very low blood pool activity was observed and the conspicuousness of lesions was notably higher with ^{18}F -DCFPyL than with the first-generation radiotracer ^{18}F -DCFBC making it a promising agent. Data from a first preliminary study comparing ^{68}Ga -PSMA-HBED-CC with ^{18}F -DCFPyL showed that ^{18}F -DCFPyL had a better tumour:background accumulation ratio, and additional lesions plausible for metastases were detected in three of the 14 patients when ^{18}F -DCFPyL was used⁸⁶.

Local detection

MRI has emerged as the imaging technique of choice for detection of prostate cancer after inconclusive or negative biopsy findings, as well as for local staging regarding capsule penetration or seminal vesicle involvement³. T2-weighted MRI sequences enable anatomical resolution of the zonal anatomy of the prostate and the delineation of suspicious areas. The addition of functional MRI sequences — namely dynamic-contrast-enhanced

(DCE) and diffusion-weighted imaging (DWI), and to a lesser extent MRI spectroscopy (termed multiparametric MRI (mpMRI)) — often enables a more accurate investigation of the prostate than MRI alone^{91–94}. Prostate cancer lesions often appear hypointense in T2-weighted sequences, but they typically show fast influx and washout of contrast material on DCE. In DWI, a reduced diffusion capacity of water molecules (reduced apparent diffusion coefficient (ADC)) owing to densely packed tumour cells as well as shifted choline and citrate metabolism on MRI spectroscopy have been observed^{27,95–98}. Furthermore, mpMRI can be used to detect aggressive prostate cancer lesions with greater sensitivity and specificity than MRI alone^{99–101}.

The introduction of whole-body hybrid PET-MRI scanners with simultaneous acquisition and exact anatomical coregistration of PET imaging and mpMRI has enabled functional and molecular information to be combined^{102,103}. PSMA ligands, as prostate-cancer-specific PET tracers, might help to visualize and delineate cancerous lesions more accurately within the prostate than choline derivatives, which are currently the most widely used PET tracers^{14,104,105} (FIG. 2). The high lesion:background ratio of the ^{68}Ga -PSMA-PET signal of suspicious lesions, as well as the information obtained from mpMRI, enables histological confirmation of prostate cancer using targeted fusion biopsies, especially in patients with previously negative findings on biopsy-sample analyses, as has been shown in preliminary studies^{106,107}. In slight contrast to these findings,



Figure 3 | ^{68}Ga -PSMA-PET-CT of a 52-year-old patient with primary prostate cancer (serum PSA value of 19 ng/ml and Gleason score 7 at biopsy). **a** | Contrast enhanced CT shows a small lymph node (6 mm) adjacent to the right internal iliac artery. **b** | PET and **c** | fused PET-CT images demonstrate intense prostate-specific membrane antigen (PSMA) expression in this lymph node. Radical prostatectomy and lymphadenectomy revealed a lymph node metastasis in the corresponding template field.

in an initial series of 13 patients Rowe *et al.*⁷¹ reported a decreased sensitivity of ^{18}F -DCFBC-PET for the detection of prostate cancer lesions compared with mpMRI; however, the specificity for detection of high-grade and more clinically significant disease was increased⁷¹. In addition, interpretation of mpMRI might be hindered by changes after biopsy sampling such as local haemorrhage or inflammation, whereas interpretation of ^{68}Ga -PSMA-PET does not seem to be influenced by biopsy¹⁰⁴. Thus, the combination of ^{68}Ga -PSMA-PET with mpMRI might improve rates of prostate cancer detection and at the same time avoid the use of unnecessary biopsy procedures. However, not all prostate cancers have substantial PSMA overexpression (~10% of primary prostate cancers do not overexpress PSMA)^{105,108}.

Primary staging

The goal of primary staging is to detect metastatic spread to the first landing sites — primarily lymph nodes, bone or other, visceral, organs. In low-risk prostate cancer metastatic spread is very unlikely; consequently, current guidelines suggest staging examinations should only be undertaken for intermediate-risk to high-risk prostate cancer^{3,11}. For evaluation of spread to lymph nodes and visceral organs CT or MRI are used, whereas bone scintigraphy is recommended for excluding bony metastases, although data from an initial study indicated that whole-body MRI might be a superior modality for detecting metastasis to bone¹⁰⁹. Naturally, staging has considerable influence on further treatment choices (such as radical prostatectomy, radiotherapy or palliative systemic treatment and the extent of pelvic lymph node dissection during surgery or planning of the radiation field, and also the consideration of multimodal therapy), exact staging assists in making the most appropriate choice.

Evaluation of lymph nodes using CT or MRI solely depends on morphological information, and metastatic lymph nodes are mainly detected on the basis of increased size. However, almost 80% of metastatic lymph nodes in prostate cancer are smaller than the threshold size of 8 mm and, therefore, cannot be detected using morphological imaging^{110,111}. The use of DWI in MRI

can help to distinguish between metastatic and normal lymph nodes^{112–114}. However, a broad overlap in DWI measurements between malignant and benign lymph nodes has been noted¹¹³. In general, the performance of CT and MRI for lymph node staging is not significantly different, as demonstrated in a meta-analysis that included 24 studies¹⁰⁸. In this meta-analysis, the pooled sensitivity was 42% and 39% and the pooled specificity was 82% and 82%, for CT and MRI, respectively¹¹¹. The authors concluded that both modalities are insufficient to reliably identify lymphatic spread, which in turn could jeopardize further treatment success.

With the introduction of PET imaging and its combination with CT or MRI hopes were raised for an increased detection rate, especially of small metastatic lymph nodes, owing to the addition of metabolic information to morphological cross-sectional imaging. Several different PET tracers, including ^{18}F -fluorodeoxyglucose, ^{11}C -choline, ^{18}F -choline, ^{18}F -fluorocholine and ^{11}C -acetate, have been studied in patients with prostate cancer^{15,115–118}. To date, the most evidence exists for choline-based tracers. However, after the first enthusiastic reports^{119,120}, a systematic review and meta-analysis conducted in 2013 revealed a only moderate pooled sensitivity of 49.2%, at the same time demonstrating a high specificity of 95%, for the detection of metastatic lymph nodes in prostate cancer¹⁶. Data from other studies showed sensitivities ranging from 33 to 45%, but confirmed high specificities of over 95% in larger patient cohorts^{121,122}. Despite its high specificity, current guidelines do not recommend PET imaging for lymph node staging of patients with primary prostate cancer with choline-based tracers as detection of metastatic lymph nodes is still hampered by the moderate sensitivity of this technique³.

The use of PSMA ligands for PET imaging might partially overcome this limitation. In a retrospective analysis of 130 consecutive patients with primary intermediate-risk to high-risk prostate cancer who underwent radical prostatectomy with template pelvic lymph node dissection, our group observed a sensitivity of 65.9% and specificity of 98.9% for lymph node staging with

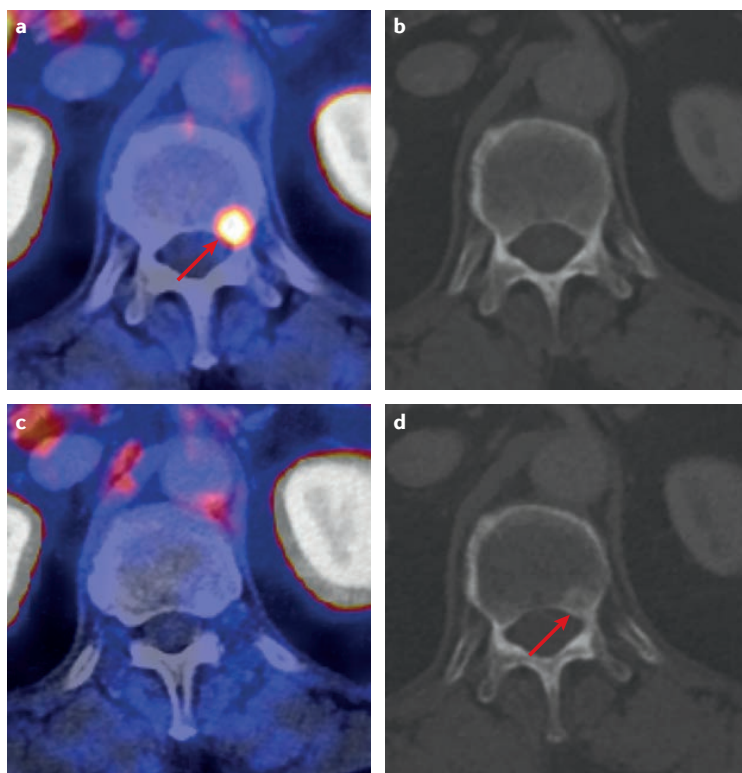


Figure 4 | ^{68}Ga -PSMA-PET-CT of a 73-year-old patient with recurrent prostate cancer after radical prostatectomy (initial Gleason score 9) and local salvage radiotherapy. Upper images are from a staging ^{68}Ga -PSMA-PET-CT examination at a serum PSA value of 3.6 ng/ml and the lower images are from a restaging examination six months later at a serum PSA value of 1.8 ng/ml. **a** | Fused PET-CT demonstrates an intense uptake in the thoracic spine suspicious for a bone metastasis. **b** | The corresponding CT reveals no morphological correlation. **c** | Fused PET-CT images, 6 months later, shows no substantial uptake of ^{68}Ga -PSMA in the lesion after external radiotherapy. **d** | CT shows a new sclerosis indicating post-therapeutic changes. PSMA, prostate-specific membrane antigen.

^{68}Ga -PSMA-PET¹⁰⁸ (FIG. 3). Of note, the patients with tumour-positive lymph nodes that were missed by PSMA-PET presented with PSMA-negative primary tumours or had micrometastases in single lymph nodes. In line with our findings, other groups have also reported a high specificity of lymph node detection with use of ^{68}Ga -PSMA-PET (REFS 75,120), although, small metastatic lymph nodes might still be missed. Furthermore, bony and visceral lesions of prostate cancer that might not be detectable using standard imaging can be visualized by ^{68}Ga -PSMA-PET (REFS 123–125). Thus, especially in patients with high-risk prostate cancer, ^{68}Ga -PSMA-PET in combination with CT or MRI could enable a complete staging of the local tumour, lymph node involvement, bone metastases and organ metastases with increased accuracy within one single examination, superseding current standard imaging and possibly improving treatment planning¹²⁵. However, published data on primary staging with PSMA ligands is still very limited and further research is needed before drawing robust conclusions.

Staging of recurrent prostate cancer

Localization of prostate cancer lesions is a major challenge in patients with biochemical recurrence. The differentiation of localized disease and metastatic spread is of great importance for further disease management, especially at low serum PSA values. For example, salvage radiotherapy in patients whose cancer recurs after radical prostatectomy is most effective at serum PSA values <0.5 ng/ml^{126,127}. Thus, radiotherapy should be initiated as early as possible in these circumstances³. Conventional bone scintigraphy or CT imaging show very limited detection rates for metastatic prostate cancer lesions at low serum PSA values at the time of biochemical recurrence after curative treatment¹²⁸; therefore, in most guidelines, imaging is recommended for patients who are symptomatic or whose serum PSA levels are >10 ng/ml^{13,17}. PET imaging with choline-based tracers has been found to improve staging and enhance detection of recurrent prostate cancer¹⁵. However, these tracers still lack the ability to identify smaller lesions or prostate cancer without increased metabolic activity — especially at low PSA velocity or serum PSA values <2 ng/ml¹⁸. Thus, PET imaging with choline-based tracers is not usually recommended at early stages of recurrence. Considering the fact that biochemical relapse is already expected in patients after radical prostatectomy with serum PSA levels >0.2 ng/ml, imaging techniques with improved sensitivity are highly desired.

In 2015, reports from two studies, with large patient cohorts, investigating ^{68}Ga -PSMA-PET were published addressing the issue of staging of recurrent prostate cancer^{73,129}. Afshar-Oromieh and colleagues⁷⁷ investigated the performance of this tracer in 319 patients with recurrent prostate cancer (226 had received radical prostatectomy) and a median serum PSA value of 4.6 ng/ml. At least one lesion typical of prostate cancer was found in ~83% of patients. The authors demonstrated detection rates of 50% for serum PSA values <0.5 ng/ml and 58% for serum PSA values from 0.5–1 ng/ml. In 42 patients, histological confirmation of lesions could be obtained. Of note, in these patients, all lesions that had a positive ^{68}Ga -PSMA-PET signal had histologically confirmed metastatic prostate cancer ($n=98$); however, 29 lymph nodes and one local relapse was missed. Tumour Gleason score and/or androgen deprivation therapy did not significantly influence detection rates.

Data from our group support these findings. In a homogeneous consecutive cohort of 248 patients with biochemical recurrence after radical prostatectomy who had a mean serum PSA value of 1.99 ng/ml, 89.5% of patients had suspicious lesions detected by ^{68}Ga -PSMA-PET-CT. For serum PSA values of 0.2–<0.5 ng/ml, 0.5–<1 ng/ml, 1–<2 ng/ml and ≥ 2 ng/ml, detection rates were 57.9%, 72.7%, 93.0% and 96.8%, respectively¹²⁹. These rates are substantially higher than those reported for choline-based PET tracers, which have reported detection rates of between 19% and 36% at serum PSA levels <1.5 ng/ml^{18,130–132}. These enhanced detection rates can be mainly attributed to information obtained from ^{68}Ga -PSMA-PET, as opposed to diagnostic CT, as it exclusively showed suspicious findings not evident on diagnostic CT in 32.7% of patients and provided

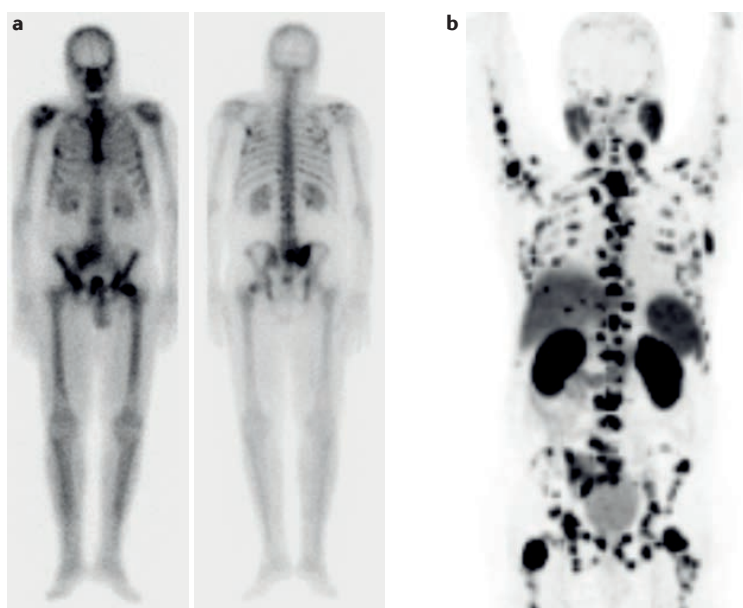


Figure 5 | Imaging of 65-year-old patient with prostate cancer and diffuse bone metastases. a | Bone scintigraphy demonstrates multiple bone metastases predominantly in the pelvis and ribs. **b** | Corresponding maximum-intensity projection of ^{68}Ga -PSMA-PET shows considerably more bone metastases than bone scintigraphy. PSMA, prostate-specific membrane antigen.

information about additional involved anatomical regions in 24.6% (FIG. 4). In comparison, morphological CT alone revealed suspicious lesions that were not apparent when assessed by ^{68}Ga -PSMA-PET in 1.2% of patients and additional involved anatomical regions in 6.9%¹²⁹. The combination of ^{68}Ga -PSMA-PET to MRI instead of CT might be able to improve detection rates in patients with very low serum PSA values (<0.5 ng/ml). In these patients, the diagnostic accuracy might be improved by combination with mpMRI, mainly owing to the fact that mpMRI has a higher detection efficacy for locally recurrent tumours than CT¹³³. Compared with absolute serum PSA value, the effects of PSA velocity and PSA doubling time on detection rates were less pronounced. A high PSA velocity ($P=0.0532$) and short PSA doubling time ($P=0.2971$) showed a tendency for increased detection rates¹²⁹. Increased detection efficacy in patients with Gleason scores >8 was observed in this patient cohort, in contrast to findings from the study by Afshar-Oromieh and colleagues⁷³.

Direct comparison of ^{18}F -fluoromethylcholine-PET with ^{68}Ga -PSMA-PET in 37 patients with recurrent prostate cancer demonstrated that ^{68}Ga -PSMA-PET is the superior modality for lesion detection⁷⁴. All lesions visible by ^{18}F -fluoromethylcholine were detected by ^{68}Ga -PSMA-PET and this tracer also revealed suspicious lesions in six patients that use of ^{18}F -fluoromethylcholine-PET missed.

Data from initial studies reveal that ^{68}Ga -PSMA-PET has a higher detection efficacy than bone scintigraphy for describing the whole extent of bone involvement^{124,125} (FIG. 5). This improved detection rate might be of relevance when monitoring is desired (such as before and after use

of ^{223}Ra -dichloride). However, a major limitation of all these studies is the lack of systematic histological confirmation in most patients. Furthermore, follow-up imaging was only available in a subset of patients. Thus, the results of these studies have to be considered with caution, although, in the meantime PSMA ligands have been successfully applied in intraoperative tracking of metastatic prostate cancer lesions, underlining the high sensitivity and specificity of PSMA ligands⁵⁰. Even small metastatic soft-tissue prostate cancer deposits could be localized and removed using PSMA-radioguided surgery for salvage procedures (FIG. 6).

Impediments to clinical application

Despite the potential advantages of PSMA-based imaging for patients with prostate cancer, several limitations have to be considered. Currently, PSMA-based imaging is not globally available, mainly owing to regulatory issues. Special national regulations that only allow the application of new drugs (which have not been finally approved) under certain restrictions mean that only a few centres in several European, South American and Asian countries, as well as Australia can use these novel tracers outside of clinical trials. Some centres in the USA and Europe use PSMA-based imaging within clinical trials (such as NCT02611882, NCT02282137, NCT02190279, and EudraCT 2014-004758-33)^{134–137}. However, a rapid spread of this new technology has been observed in countries where application of PSMA-ligands for imaging is permitted. The issue of reimbursement by health-care providers, which mostly does not cover PSMA-based imaging as it is still considered experimental, is another limitation. Thus, the design and execution of prospective trials are a high priority so that evidence required to enable implementation of this promising imaging technology into clinical guidelines is obtained.

Conclusions

Imaging with PSMA-PET has the potential to influence the management of patients with prostate cancer¹³. Optimizing the labelling of PSMA inhibitors might also be of interest as initial reports suggest that ^{18}F -labelled PSMA inhibitors might be advantageous, owing to their increased availability, and the possibility that they will have a positive influence on image resolution.

PSMA-PET imaging might improve detection, localization or exclusion of cancerous foci within the prostate. In this setting, combination of PSMA-PET with mpMRI instead of CT is highly preferable, owing to the excellent anatomical and zonal resolution of the prostate obtained by T2-weighted MRI sequences. Furthermore, functional MRI sequences (mainly DWI and DCE sequences) can be used to detect and localize suspicious lesions. In combined hybrid PET-MRI, PSMA-PET provides additional molecular information by direct detection and localization of PSMA-positive tissue, which might be useful — especially in patients who have had several biopsy samples taken, which have proven negative on analysis, where detection or exclusion of prostate cancer is warranted. In these cases, the information obtained from PSMA-PET-MRI can be used to perform targeted biopsies and, therefore, increase



Figure 6 | ^{68}Ga -PSMA-PET-CT of a 74-year-old patient with recurrent prostate cancer (initial Gleason score 7) after radical prostatectomy and local salvage radiotherapy with rising serum PSA value (1.76 ng/ml at the time of assessment). **a** | Contrast-enhanced CT shows a mass in the area of the former left seminal vesicle having residual tissue, reactive fibrosis or recurrent disease. **b** | PET and **c** | fused PET-CT images demonstrate intense ^{68}Ga -PSMA uptake, indicative of a locally recurrent tumour. Salvage PSMA-radioguided surgery revealed soft-tissue poorly differentiated adenocarcinoma of the prostate (Gleason score 7) including a seminal vesicle with a cribriform carcinoma, PSMA, prostate-specific membrane antigen.

the diagnostic performance of prostate biopsy sample analysis. However, the availability of combined PET-MRI and the high costs associated with this approach are limiting factors that preclude the widespread use of this technology.

Evaluation of metastatic spread to lymph nodes, bone or visceral organs in patients with primary intermediate-risk or high-risk prostate cancer might be improved by PSMA-PET imaging. In these patients PSMA-PET-MRI or PSMA-PET-CT enables a whole staging procedure to be performed in one single examination, rendering further cross-sectional imaging or bone scintigraphy unnecessary. Furthermore, data from currently published studies suggest that ^{68}Ga -PSMA-PET imaging increases diagnostic accuracy for primary staging of patients with prostate cancer. Thus, the results of PSMA-PET imaging might influence treatment selection and modify therapy approaches.

Currently, recurrent prostate cancer is the main indication for the use of PSMA-PET and the majority of published data focus on this setting. In patients who have

undergone radical prostatectomy, PSMA-PET improves detection of metastatic prostate cancer compared with conventional cross-sectional imaging or bone scintigraphy. Furthermore, it increases the detection of lesions even at serum PSA values <0.5 ng/ml compared with conventional imaging or PET examination with different tracers. As salvage radiotherapy is most effective at low serum PSA values, PSMA-PET imaging could be used to optimize radiotherapy planning by defining the target lesions or areas that are most appropriate for boost radiotherapy.

PSMA-PET imaging could also facilitate new salvage treatment options by identifying patients with oligometastatic disease that are suitable for PSMA-radioguided surgery. The high uptake of PSMA-inhibitors in castration-resistant prostate cancer means that these ligands are good candidates for facilitating guided endoradiotherapy in patients with metastatic prostate cancer. Hereby, PSMA inhibitors could potentially be used as theranostic agents in patients with metastatic prostate cancer, to visualize and treat these lesions at the same time.

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Author contributions

T.M. and M.E. contributed equally to the manuscript, researched data for and wrote the article. All authors made a substantial contribution to discussions of content and edited the manuscript before submission.

Competing interests statement

T.M. declares a familial association with Celgene® (Celgene Corporation, USA); grants or funding from Acclity® (KCI Licensing, Inc.), Bayer® (Bayer Aktiengesellschaft, Germany) and Takeda Oncology® (Takeda Pharmaceutical Company Limited, Japan); consultation for DLR® (Deutsches Luft- und Raumfahrtzentrum, Germany) and honoraria from Astellas® (Astellas US LLC, USA), Janssen Cilag (Johnson & Johnson, USA) and Sanofi® (Sanofi Corporation, France). M.E. declares grants or funding from Bayer® and honoraria Astellas® and Janssen Cilag. M.S. and J.E.G. declare no competing interests.