New frontiers in prostate cancer imaging: clinical utility of Prostate Specific Membrane Antigen Positron Emission Tomography

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Abstract

Prostate specific membrane antigen Positron Emission Tomography (PSMA PET) is a relatively new method of imaging prostate cancer that increases diagnostic accuracy in detecting and guiding management in various stages of the disease pathway.

Gallium -68 labelled PSMA PET has increased the sensitivity of detection of disease recurrence at low PSA levels, thus allowing an optimal window for salvage treatment.

Apart from its use in disease recurrence, PSMA PET has the potential for increasing sensitivity and specificity for primary tumour localisation and in detecting lymph node disease, leading to a more accurate initial staging of the condition.

In advanced disease, the use of PSMA PET may be able to assess response to treatment and also guide treatment with radionuclide therapy. Newer ligands under development might provide avenues for theranostic or personalised therapy applications with early data showing high PSA response rates.

The rate of translation of PSMA PET into clinical practice has been remarkable. The use of this modality is likely to increase with future efforts to modify the radiotracer including ^{18}F labelling to improve availability.

Keywords

PSMA PET, Prostate cancer, imaging, theranostics, radiotracers

Introduction

The diagnosis and management of prostate cancer (PCa) is widely dependent on imaging tools to achieve accuracy and precision. Currently, many centres rely on multiparametric MRI (mpMRI) and planar bone scintigraphy as the most often used imaging modalities. Despite advances in imaging, the diagnosis and follow-up of PCa continue to remain challenging. Positron emission tomography (PET) CT has had an increasing role in PCa management in recent years with the availability of ^{11}C and ^{18}F choline tracers. ^{11}C has a short half-life of 20 minutes requiring the presence of a cyclotron on site for synthesis and ^{18}F has a half-life of approximately 110 minutes. The short half-life of ^{11}C limits its distribution and utility. Moreover, Choline PET suffers from limited sensitivity in detecting disease at low PSA levels [1]. These limitations, in turn, have led to the search for newer PET tracers and imaging biomarkers to help increase sensitivity and accuracy of imaging in PCa detection.

Prostate Specific Membrane Antigen (PSMA) is a type II transmembrane glycoprotein, typically associated with the apical membrane, with transfer to the ductal luminal surface in prostate tissue and highly expressed on the surface of prostate tumour cells [2]. When used as a target for PET imaging with Gallium 68 (^{68}Ga) labelling, the normal physiological distribution includes salivary glands and the kidneys which demonstrate relatively intense tracer uptake, and the lacrimal glands, liver, spleen and the intestines which have moderate activity. Excretion of unbound tracer occurs via the urinary tract [3]. PCa causes a massive overexpression of PSMA in tumour tissue, allowing radiolabeled agents targeting this protein a greater sensitivity in tumour

detection. However, non-prostatic tumours also demonstrate PSMA expression in areas of neovascularity including renal, bladder, breast and colon cancer [4-9]. Despite expression seen on other sites, PSMA has been developed as a radiotracer and has entered into clinical practice as a biomarker for the detection of PCa and its metastases.

^{68}Ga-PSMA is produced using a 68 Germanium (Ge)/68Ga radionuclide generator. After injecting 1.8-2.2MBq/kg body weight as an IV bolus, PET acquisition begins approximately 60 minutes after tracer injection. Depending on scanner specifications, there are variations in the length of time needed for each bed position (body section typically divided into four, beginning at the mid thighs and moving towards the vertex), but in modern scanners, 3-4minutes per bed position is typical. Following this, a low dose CT scan images the same volume for attenuation correction and anatomic localisation. The technique can vary in numerous ways to improve image quality, including using iv iodinated contrast medium with the CT, administering a diuretic (frusemide) at the time of radiotracer injection and rectal filling with a negative contrast medium [10].

Applications of PSMA PET in biochemical recurrence of PCa

PCa patients who have had radical prostatectomy or radiotherapy have a risk of developing recurrent disease, defined by a rise in serum PSA, with specified criteria in the context of previous treatment. Once PCa recurrence is suspected, the search for disease begins with subsequent management dependent on metastatic extent. Recurrence may be in the prostate or prostatectomy bed, within pelvic or more remote lymph nodes, within the skeletal system or other less common distributions including lung and soft

tissue deposits. Detection of localised disease at low PSA levels allows an optimal range of treatment strategies to be offered, particularly essential as salvage radiotherapy in recurrence post-prostatectomy is most effective at serum PSA <0.5ng/ml [11,12].

Disease assessment in the context of biochemical recurrence forms the bulk of literature in the use of ^{68}Ga-PSMA PET. The clinical need for a sensitive tool for early detection of recurrence exists because current modalities struggle to identify disease at a low PSA level successfully. For example, choline PET tracers have a detection rate ranging from 19-36% when serum PSA is below 1.5ng/mL [13,14,15]. *(*Fig 1)

Published studies on imaging in this clinical setting have suffered from the limitation of lack of histological correlation of most sites determined positive for the disease by imaging, as this would be impractical in many cases. When compared with choline PET, PSMA was found to be superior in disease detection in 37 patients. PSMA PET was able to detect all PCa lesions demonstrated on Choline PET as well as additional sites of tumour, identifying 86.5% of patients with at least one site of disease characteristic for PCa compared with 70.3% with Choline PET [16]. Similarly, Morigi et al. have shown findings of ^{68}Ga-PSMA superiority over choline in 38 patients, where on lesion-based analysis, ^{68}Ga-PSMA detected significantly more lesions than (18)F-fluoromethylcholine (59 vs. 29 respectively, $P < 0.001$) [17]. (Fig 2).

The first large patient cohort study involved 319 patients with biochemical recurrence. In this study, 82.8% of ^{68}Ga-PSMA scans were positive, and the probability of detecting disease increased with higher PSA levels. For example, there was a 50% likelihood of positive scan at PSA <0.5 and 60%

when PSA was 0.5-1 [18]. This study showed no significant association of positive scans with PSA doubling times, although a tendency towards positive scans with unfavourable PSA kinetics was noted. Others have shown a significant relationship correlation, although less marked than the correlation with PSA [19].

There is evidence from preclinical studies that higher Gleason grade tumours express more PSMA receptors and would help explain why a higher Gleason score correlates with positive PSMA imaging [20].

Impact on primary staging

Multiparametric MRI is the gold standard of imaging based staging of primary prostate cancer. The combination of T2 sequences, diffusion weighted imaging and dynamic contrast enhancement has become widely used with a 1-5 score (PIRADS) of confidence of tumour detection. However, the accuracy in detecting disease on MRI reduces with small volume or low grade (Gleason 3+3) disease [21, 22]. Recently, ^{68}Ga-PSMA has been evaluated in simultaneous PET and MRI scanners and has shown to be of use in detecting disease, with complimentary findings from both modalities. Although very limited data exists on the use of primary tumour evaluation, initial reports have suggested potential key benefits of PSMA including a lack of influence of uptake in the post-biopsy setting compared to MRI. Prostatic tumour foci were predicted correctly in 92.9% of high-risk prostate cancer patients undergoing radical prostatectomy [23]. However, a potential limitation is that up to 10% of primary prostate tumours may be PSMA negative, although no data exists to establish the receptor status of tumour cells in these patients. Recognised potential sources for false negative results include tumours located adjacent

to areas of high physiological tracer uptake, small tumours and those with neuroendocrine differentiation seen in high grade and high stage disease[24]. Overall, there is an increase in sensitivity and specificity when using ^{68}Ga-PSMA PET and mpMRI rather than using the modalities alone for primary tumour localisation, especially when used in combination for guiding biopsy or in the re-evaluation of cases where mpMRI alone has failed to identify the site of disease. (Fig 3).

Previous studies have shown that up to 98% of lymph node metastases from prostate cancer demonstrate very high levels of PSMA [25]. Promising results have also been published recently using PSMA in nodal evaluation for initial staging. In 130 patients with intermediate to high-risk prostate cancer treated with prostatectomy and pelvic lymph node dissection, ^{68}Ga-PSMA was shown to have a sensitivity of 65.9% and specificity of 98.9% for lymph node staging [26]. These rates compare well with the reduced sensitivity of choline PET (49.2%) with a similar high specificity of 95% and the even poorer sensitivity and specificity for CT (42% and 82%) and MRI (39% and 82%) respectively [27].

However, micrometastatic nodal disease may still escape detection. One study retrospectively compared pre-operative ^{68}Ga-PSMA PET with histological findings after radical prostatectomy. Lymph node metastases were present in 12 out of 30 patients. ^{68}Ga-PSMA PET was found to have an excellent specificity (100%) with no false positive findings“. ^{68}Ga-PSMA PET could correctly identify only 4 of the 12 confirmed cases, although the size of the histologically positive nodes not identified was significantly smaller (a median histologically positive node size of 4.3mm not detected on PET,

compared to a median histologically positive node size of 13.6mm correctly identified). The study had several limitations, not least a lack of involvement from nuclear medicine specialists and a small sample size [23,28]. Furthermore, there was no proof that the nodes deemed false negative contained tumour cells expressing PSMA receptors.

PSMA, therefore, appears to be the most accurate available method of imaging based nodal assessment, with exciting potential future use in combination with state of the art multiparametric MRI sequences.

Although planar bone scintigraphy has long been the standard for assessing for bone metastases, whole-body MRI has been shown to be of superior accuracy in bone metastasis detection [29]. The combination of PSMA with whole body MRI, to detect nodal, bone and other sites of disease detection offers a possible one-stop approach to staging, although extensive studies including assessment of cost-effectiveness would be necessary to bring forward such a move into clinical practice. (Fig 4).

A few studies have compared the diagnostic accuracy of ^{68}Ga-PSMA PET/CT with ^{68}Ga-PSMA PET/MRI. In a study of 20 patients, Afshar-Oromieh, et al. concluded prostate cancer diagnosis was easier and more accurate on PET/MRI than PET/CT [30]. Unclear findings on PET/CT were able to be clarified on PET/MR, although the latter were performed at a later uptake time (three hours rather than an hour post injection) which may have aided disease detection by increased tracer accumulation in the tumour over time [29]. Similarly, Freitag et al. demonstrated ^{68}Ga-PSMA PET/MR to be reliable and accurate when compared to PET/CT for node and bone lesion detection in 26 patients [31].

Bone metastases tend to demonstrate less avid ^{68}Ga-PSMA uptake than nodal sites of disease [32] However, lesions are still clearly positive on PET. In a study evaluating 28 bone metastases with ^{68}Ga-PET/CT and PET/MRI, two of these lesions were not demonstrated on the CT component of PET/CT but were visible in the MR element, and all lesions were PET positive [31].

Future trends

Although ^{68}Ga-PSMA PET has rapidly entered clinical practice for use in the setting of biochemical recurrence, there is a need for well-designed phase III studies to prove this is best practice. Other potential uses will also require further research as detailed below.

Diagnostic and treatment applications in advanced disease

In patients who have failed conventional therapy or have advanced metastatic disease, PSMA may be able to guide other treatment options including chemotherapy or radionuclide therapy.

Semiquantitative assessment of metastatic sites with metrics based on Standardised Uptake Values (SUV) and metabolic tumour volume compared with post therapy appearances may offer a method for assessing response to treatment.

Personalised therapy and theranostic applications

PSMA ligands can be labelled with ^{188}Re (Rhenium) or ^{177}Lu (Lutetium) and can act as a theranostic agent (providing diagnostic based therapy for individual patients) for radio-guided surgery or endo-radiotherapy. Although these agents are the subject of clinical trials, such compounds may be offered currently under ‘compassionate use’ circumstances. Recent studies have shown promising results with ^{177}Lu PSMA therapy, with a PSA response rate

of 80% after the first cycle in a study of 24 patients and 70% in another study of 30 patients. However, the response may only be a short-term benefit in some patients, with only 70% and 50% having an ongoing response in the above two studies [33, 34].

New agents

As ^{68}Ga is generator produced, there is a movement towards developing a suitable ^{18}F (Fluorine) labelled compound which could be mass produced via cyclotron and become more widely available. Preliminary studies in humans have demonstrated the feasibility of these tracers.

^{18}F-DCFBC (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-(18)F-fluorobenzyl-L-cysteine ((18)F-DCFBC),is another radiotracer that targets PSMA. ^{18}F-DCFBC has been evaluated and shown to identify more suspicious bone lesions than bone scintigraphy or CT. This agent may also distinguish between high and low-grade primary prostate lesions [35, 36].

A second generation ^{18}F labelled agent, ^{18}F-DCFPyL(2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid ([^{18}F]DCFPyL) has been shown to demonstrate greater metastatic and primary lesion conspicuousness than ^{18}F-DCFBC and also when compared with ^{68}Ga-PSMA [37,38].

Future work may include modification of the PSMA molecule itself which could alter function and increase sensitivity. Clearly, larger prospective studies would be needed to confirm which form of PSMA ligand would be optimal for clinical use.

Conclusion

There is unequivocal evidence that ^{68}Ga-PSMA is highly sensitive and specific for prostate cancer disease detection, more so than any currently used imaging modalities and tracers and this has lead to a rapid acceptance into clinical practice. PSMA PET has an important potential role in routine clinical management at multiple stages of the patient pathway. The commonest indication to date involves disease detection in the setting of biochemical recurrence although there may be opportunities for a role in initial disease evaluation and restaging or response assessment in advanced disease, with possible one-stop approaches using state of the art PET/MRI. Currently, ongoing clinical trial data have shown that PSMA ligands may also be labelled to act as theranostic agents, with initial data showing high rates of PSA response.

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Compliance with ethical standards

Conflict of interest: The authors declare they have no conflicts of interest in this study.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Human and animal rights: This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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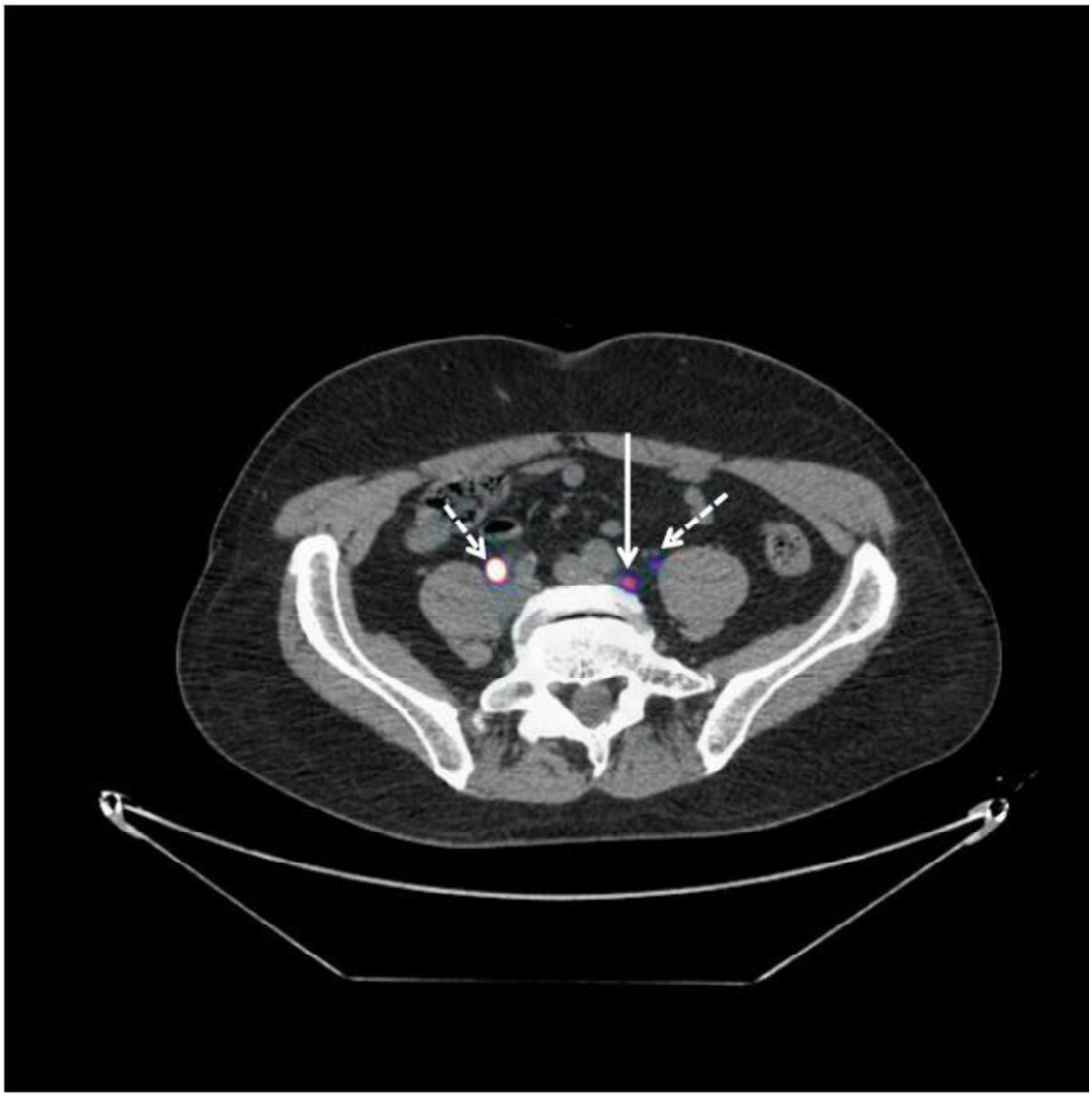
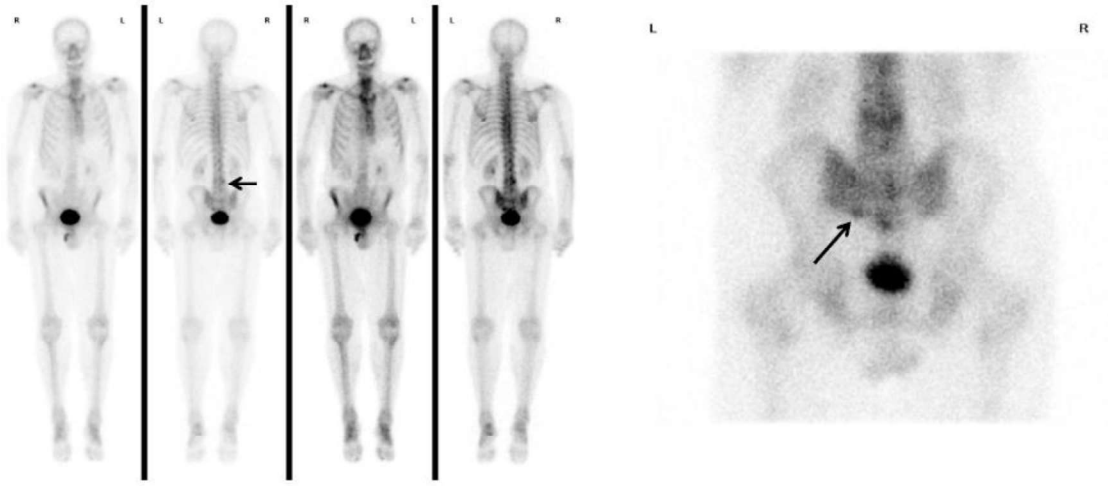
Figures

Figure 1



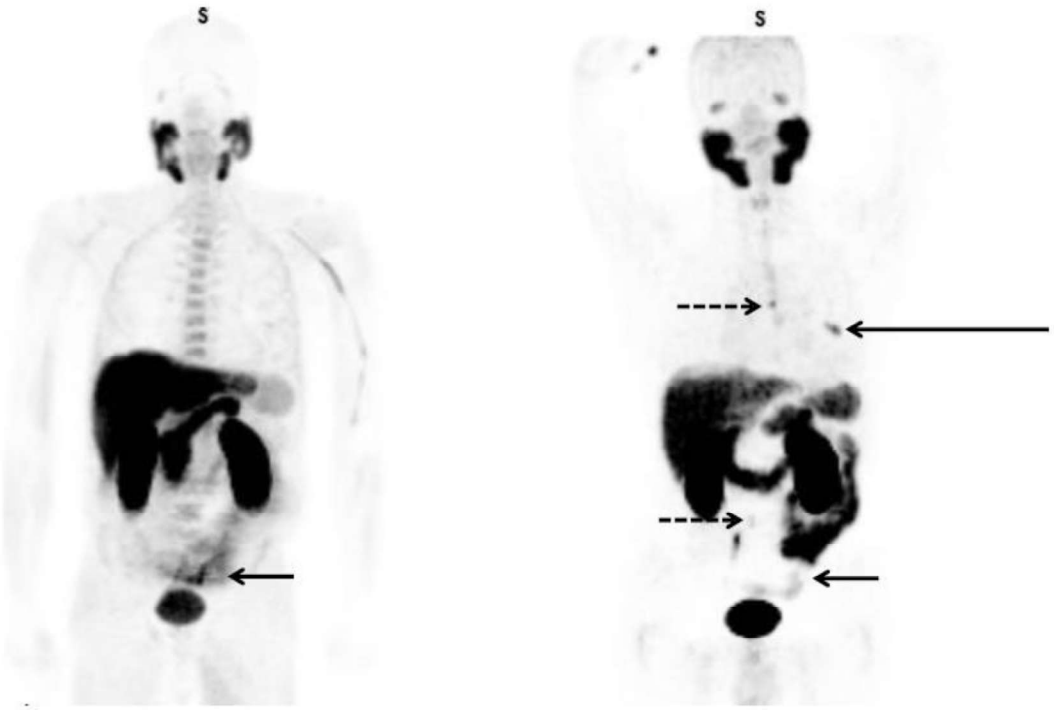
This 66 year old man with Gleason 4+5 disease and previous prostatectomy and radiotherapy had a rising PSA (1.9). ^{68}Ga-PSMA PET/CT showed small volume PSMA avid retroperitoneal nodal recurrence. The solid arrow demonstrates an avid node. The dashed arrows indicate physiological tracer activity in the ureters.

Figure 2a



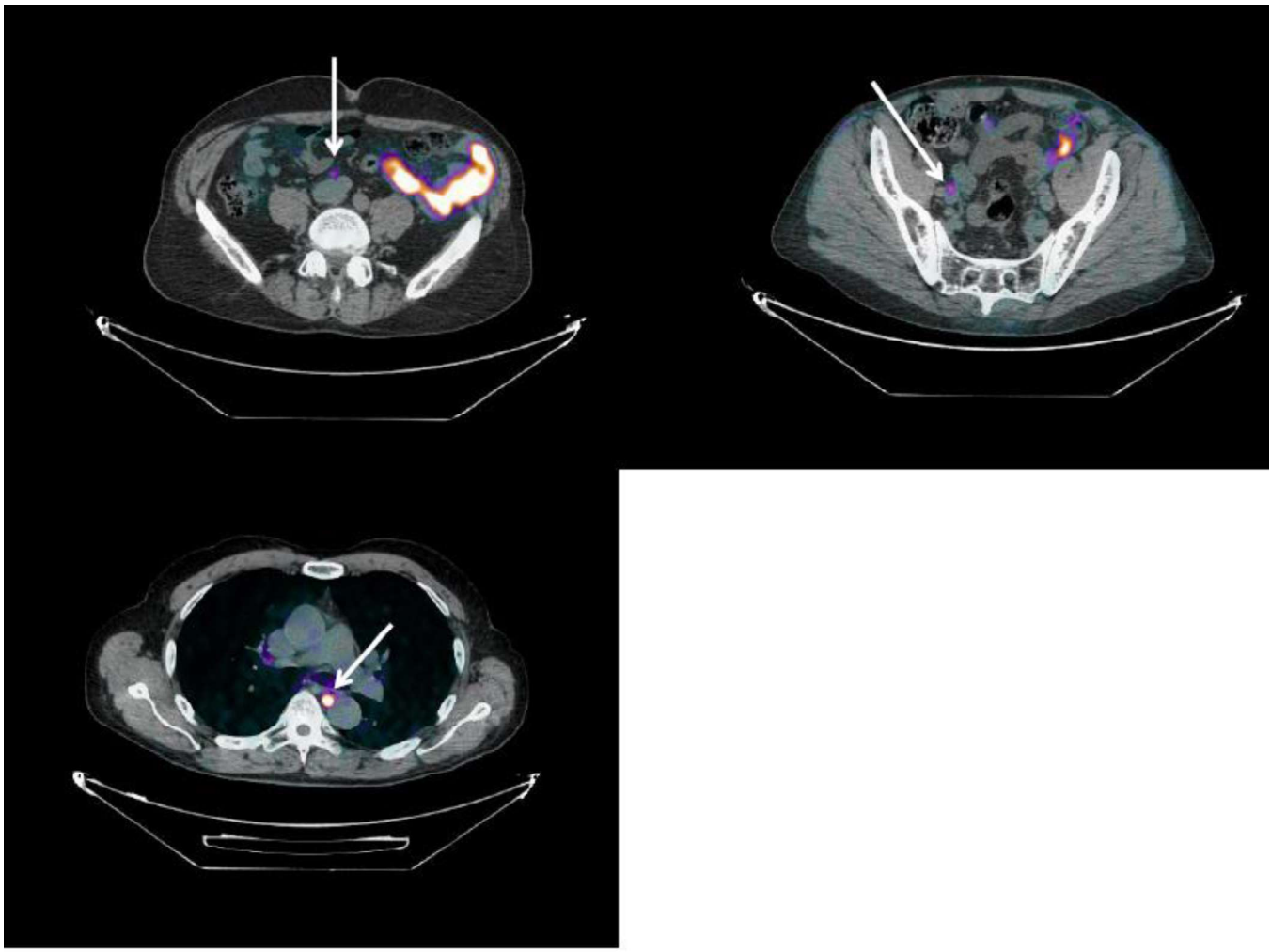
A 68-year-old man with Gleason 4+4 disease treated with EBRT and then with salvage HIFU for recurrence in 2011. Now presenting with a rising PSA (29), Technetium99m methylene diphosphonate bone scintigraphy showed probable degenerative change at the right side of L3/4 and inferior aspect of the left sacroiliac joint (black arrows).

Figure 2 b



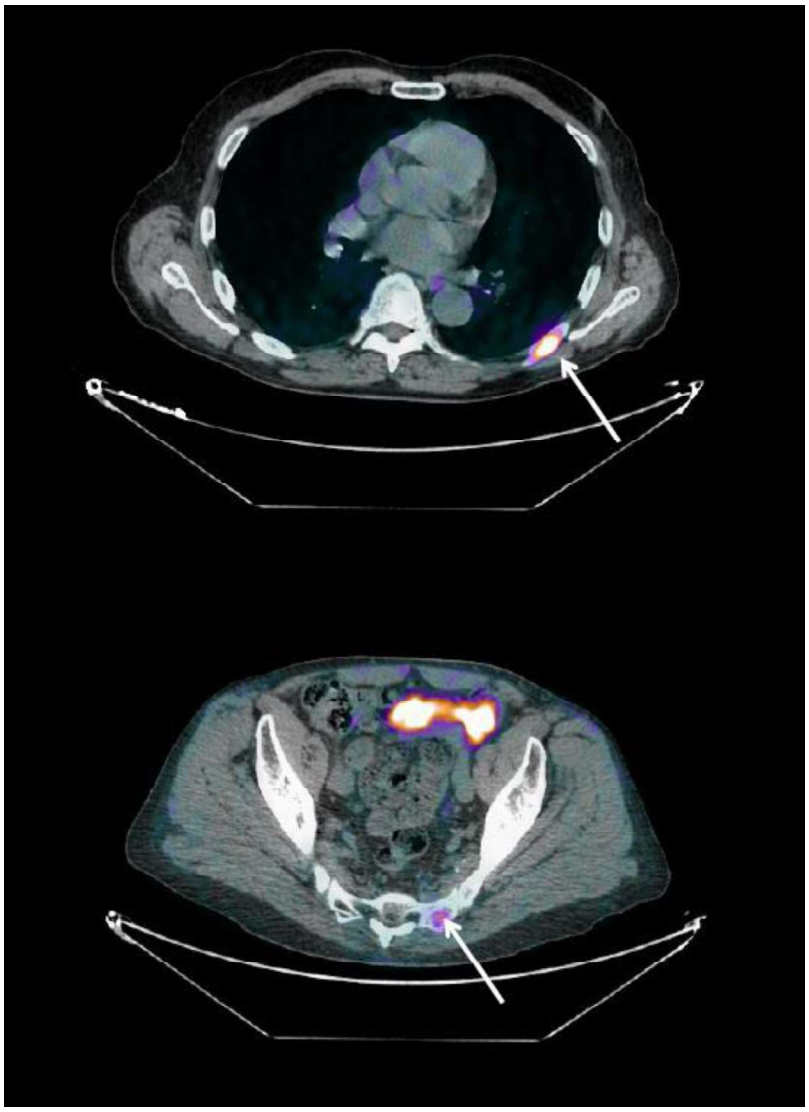
An ^{18}F Choline PET study (left image) showed possible disease in the left hemi-sacrum (black arrow), but no other sites of disease. Within a four- week interval, the patient had a ^{68}Ga-PSMA PET/CT (right, image) which confirmed left sacral disease (black arrow) but also demonstrated new metastases including the left 7th rib (long black arrow) and nodal sites (dashed arrows) as detailed in figure 2c.

Figure 2c



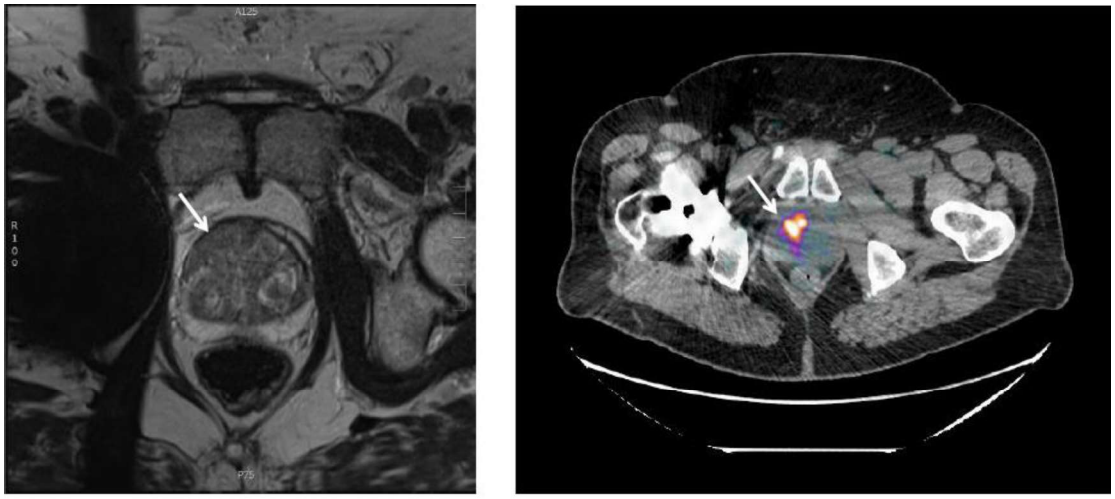
Axial fused images from the ^{68}Ga-PSMA PET/CT study showing retroperitoneal nodal disease (top left), right external iliac node (top right) and a posterior mediastinal node (bottom left)

Figure 2d



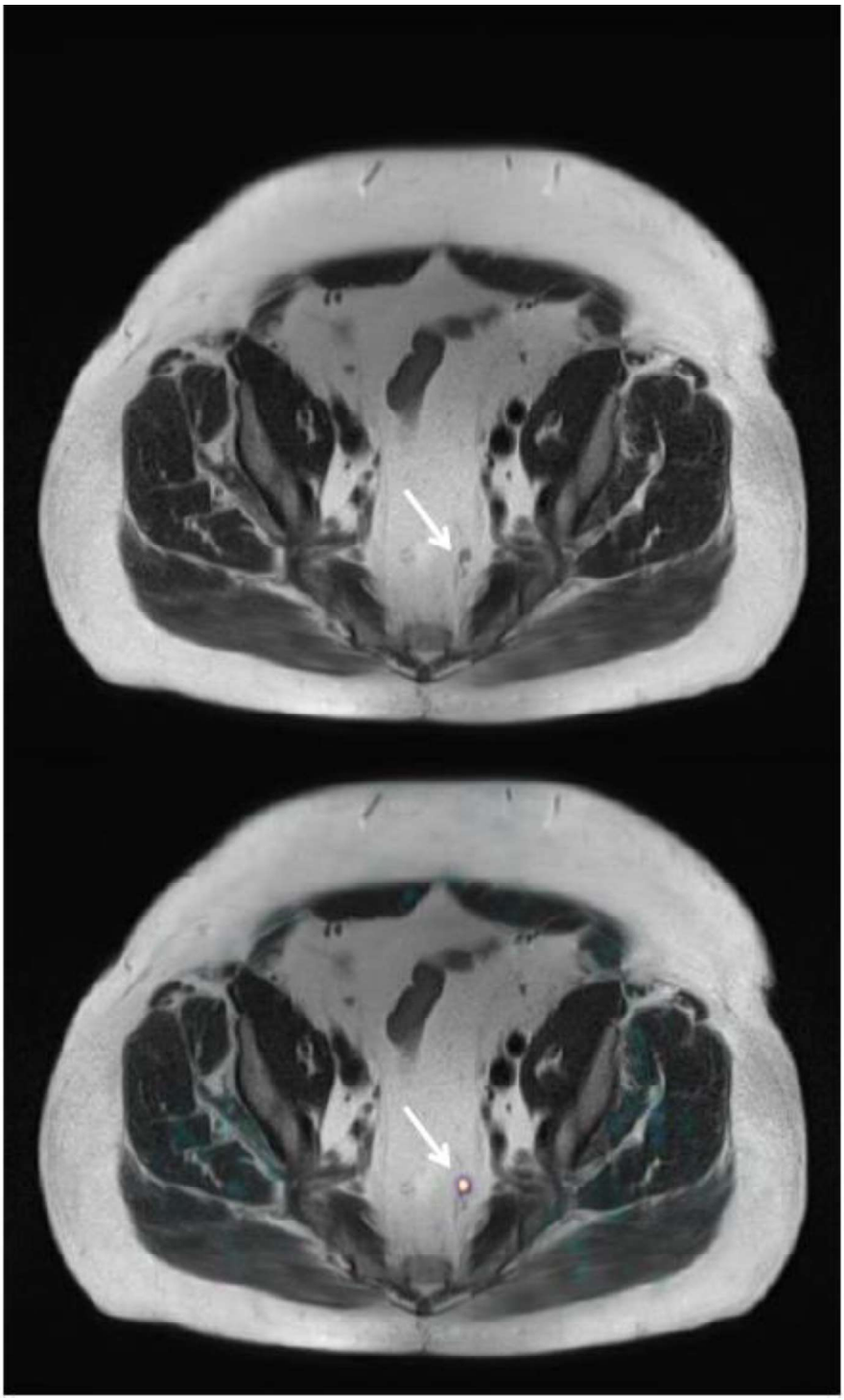
Axial fused ^{68}Ga-PSMA PET/CT images showing left 7th rib disease (top image) and left sacral ala disease (bottom image).

Figure 3



This 72-year-old man underwent initial MRI assessment for elevated PSA of 22. (September 2015). Artefacts from the right hip prosthesis rendered diffusion and dynamic contrast enhanced images non-diagnostic; however, there was a possibility of disease in the right TZ (white arrow on the left image, axial T2 small field of view MRI image). In Feb 2016, a prostate biopsy revealed Gleason 3+4 disease with a focus of 5. PSMA PET (March 2016) revealed tracer-avid tumour in the right TZ but no other sites of disease (right image, white arrow on the fused ^{68}Ga-PSMA PET/CT)

Figure 4



A 68-year-old man who had Gleason 3+4 disease treated with prostatectomy and prostate bed RT a year later. Now with a rising PSA (1.24), ^{68}Ga-PSMA PET/MRI revealed small volume presacral nodes which were tracer avid.

The upper image is an axial T2 HASTE MRI image with the white arrow indicating a small volume lymph node (4mm in short axis diameter). The lower image is a fused T2 HASTE and ^{68}Ga-PSMA attenuation corrected image showing the small node is PSMA avid.