

More advantages in detecting bone and soft tissue metastases from prostate cancer using ^{18}F -PSMA PET/CT

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Prostate cancer (PCa) is the most common solid cancer affecting men worldwide [1]. Serum prostate-specific antigen (PSA) is at present the most commonly used biomarker for PCa screening, as well as a reliable marker of disease recurrence after initial treatment. Bone metastases (BM) are present in advanced stages of the disease. Imaging of BM is important not only for localization and characterization, but also to evaluate their size and number, as well as to follow-up the disease during and after therapy. Bone metastases formation is triggered by cancer initiating cells in the bone marrow and is facilitated by the release of several growth factors. Although BM from PCa are very heterogenic, the majority of them are described as “osteoblastic”, while pure “osteolytic” metastases are very rare [1, 2].

The PSA levels, along with other parameters, may determine the risk of having BM. A classification report, which is currently in use, divides patients into three categories according to the risk of having BM: low risk (PSA < 10 ng/mL, clinical stage T1-T2a, Gleason Score ≤ 6), intermediate risk (PSA 10.1-20 ng/mL, clinical stage T2b-T2c, Gleason Score = 7) and high risk (PSA > 20 ng/mL, clinical stage T3a or higher, or Gleason Score ≥ 8). Even though PSA remains the only biomarker of this disease in clinical practice, it is not always analogue with the severity of the disease and should be evaluated along with the clinical and diagnostic imaging findings [1-5].

Detection of BM is not always easy, as there may be unexpected sites and occult metastases. The clinical importance of revealing BM in patients with PCa is to determine the overall survival of the patients and their quality of life, as BM may lead to high morbidity and mortality. There are many options of treating BM, such as chemotherapy, immunotherapy, external beam radiotherapy, bone modifying agents and recently prostate-specific membrane antigen (PSMA) targeted therapies. Another potential therapy is radioguided surgery, in patients with occult and/or focally recurrent PCa. Such a single occult metastasis causing very high levels of PSA has been presented using technetium-99m ($^{99\text{m}}\text{Tc}$) labeled PSMA imaging [1, 6].

Diagnosis and staging of PCa mostly relies on the morphology of imaging, using computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/CT (PET/CT) using fluorine-18-fluorodeoxyglucose (^{18}F -FDG) [7].

The radiopharmaceuticals used in Nuclear Medicine for BM in PCa are: a) those that target lesions, such as $^{99\text{m}}\text{Tc}$ -phosphonates, ^{18}F -sodium fluoride (^{18}F -NaF) and b) those that target the cancer cells, such as ^{18}F or carbon-11 (^{11}C)-choline, ^{18}F -FDG and ^{18}F or gallium-68 (^{68}Ga)-PSMA [1].

Bone scan with $^{99\text{m}}\text{Tc}$ -phosphonates is widely used for the evaluation of bone metabolism in patients with PCa. It is a low cost, widely available radiopharmaceutical having the advantage of a whole body evaluation. Planar and single photon emission tomography (SPET) may also be applied. The sensitivity of the whole body scan (WBS) ranges from 75%-95%, while the specificity is lower, ranging from 60%-75% due to false positive findings in benign conditions (arthritis, inflammation etc) who also have increased bone metabolism [8]. Sensitivity and specificity however, perform better (96% and 94% respectively) when SPET and SPET/CT techniques are applied. Of course, bone marrow metastases cannot be detected in a WBS. The PSA marker is used to predict the pre-test probability of BM and in case of a bone scan several retrospective analyses showed that PSA levels < 20 ng/mL can exclude with high probability a positive WBS, with a high negative predictive value (almost 99%) [9]. The European Association of Urology (EAU) guidelines state that a bone scan can be omitted in patients with PSA levels < 20 ng/mL and with a Gleason Score ≤ 7 [1, 10].

Imaging with ^{18}F -NaF PET/CT is characterized by high and rapid bone uptake, minimal serum protein binding and rapid blood clearance which lead to a fast and high target to background ratio with a short acquisition time (30 minutes). Sensitivity and specificity for the detection of BM in high risk PCa patients is almost 100%. The main advantages provided by ^{18}F -NaF PET/CT are the better imaging quality along with a whole body acquisition and the fusion technique [11].

Fluorine-18-choline and ^{11}C -choline PET/CT came to practice lately, reflecting the cell membrane metabolism. Choline is an

essential component of phospholipids and is trapped in the cells after a phosphorylation by a choline kinase. The sensitivity and specificity of ^{18}F -choline PET/CT for detecting BM in patients with PCa is reported to be 79% and 97% respectively. However, the performance of choline PET/CT seems to be dependent of the levels of the PSA, in cases of biochemical recurrence and reaches about 75% in those PCa patients with PSA levels $>3\text{ng/mL}$, with a poor performance when the PSA level is low [1, 12].

Fluorine-18-FDG is the most commonly used radiotracer in PET/CT, however has a little value in staging and restaging of PCa. Because of its low sensitivity ^{18}F -FDG is trapped in cancer cells through the activation of the glycolytic pathways and in case of BM is an index of increased glucose metabolism in PCa cells rather than in bone lesion per se. Osteolytic lesions show more increased metabolic activity than the osteoblastic lesions and are better revealed with ^{18}F -FDG. Therefore, ^{18}F -FDG PET/CT is suggested to be performed only in selected patients with PCa, those with most aggressive tumors and high Gleason score [1, 13].

Fluorine-18-PSMA PET/CT

The need of a more sensitive and specific agent has been evident. Prostate specific monoclonal antibody (PSMA) is a folate hydrolase cell surface glycoprotein. It is mainly expressed in four tissues of the body, including prostate epithelium, the proximal tubules of the kidney, the jejunal brush border of the small intestine and ganglia of the nervous system [14, 15]. So consequently may in some cases be expressed in cancers other than PCa and also in benign processes. It is localized in the cytoplasm and the apical side of the prostate epithelium that lines prostatic ducts. In case of malignant transformation, PSMA is transferred from the cytoplasm to the luminal surface of the prostatic ducts and thus becomes membrane bound. It has a unique three-parts structure, an external portion, a transmembrane portion and an internal-cytoplasmatic portion [16]. Prostate specific monoclonal antibody is also upregulated and thus overexpressed in most PCa, but weakly expressed in normal prostatic tissue. Imaging by PSMA PET/CT has been shown to detect sites of disease recurrence at lower PSA levels than conventional imaging. The PSMA overexpression is even present when the cell becomes castrate-resistant and that is the reason why it is the most favorable target for PET imaging. Prostate cancer expresses 100 to 1000 times more PSMA than normal tissue and is increasing even more in higher grade tumors as well as in increased castrate resistance [17, 18]. Therefore, PSMA represents an excellent target for both diagnostic imaging and endoradiotherapy of PCa [16].

For diagnostic purposes PSMA ligands, mainly small-molecule inhibitors, are most commonly labeled either with ^{68}Ga or ^{18}F . The ^{18}F -PSMA-1007 (((3S,10S,14S)-1-(4-(((S)-4-carboxy-2-((S)-4-carboxy-2-(6- ^{18}F -fluoronicotinamido) butanamido) methyl phenyl)-3-(naphthalen-2-ylmethyl)-1,4,12-trioxo-2,5,11,13-tetraazahexadecane- 10,14,16-tricarboxylic acid)) seems to be more favorable among other ^{18}F -PSMA ligands candidate compounds because it demonstrates high labeling yields, better tumor uptake and non-urinary background clearance. On the contrary, ^{68}Ga -PSMA is rapidly excre-

ted via the urinary tract resulting in intense accumulation in the bladder, thus, obscuring the prostate [19, 20]. Compared to ^{68}Ga , ^{18}F has many advantages such as it is produced in larger amounts, it has a longer half life and a higher physical spatial resolution [20, 21]. The short half-life of ^{68}Ga relative to ^{18}F (68 vs. 110 min) makes ^{68}Ga -PSMA inconvenient for longer transport, so that it is almost mandatory to use local gallium generators, which have a higher cost and lower yields at the end of their first half-life. Each generator provides only one or two elutions per day and it requires separate syntheses at different times of the day in a local radiopharmacy. Furthermore, the resolution of ^{68}Ga -labeled tracers is physically limited because of positron range effects. In contrast, ^{18}F labels avoid these intrinsic difficulties and can be produced at high yields in central cyclotrons [20, 21].

Fluorine-18-PSMA-1007 has been recently used by us in the Nuclear Medicine Department of "Evangelismos" general hospital of Athens and our experience so far showed favorable results, with high image resolution acquisitions and lesions which showed PSMA avidity. Fluorine-18-PSMA-1007 PET/CT imaging was carried out with a dual phase protocol, consisting of two separate scans [17]. One (early scan) at 60 min post injection starting from the diaphragm to the middle of the thighs and the late scan at 180min from the dome of the skull to the knee joints. Patients were asked to urine before the examination. Images were acquired with a scan time of 3min per bed position on a General Electric PET/CT system and the image reconstruction was performed by the standard software method provided by the manufacturer. A low dose CT scan, without a contrast agent, was performed before the PET scan in order to be used for the attenuation correction. Administered activities were calculated based on the department's protocols with a suggested injected activity of 4MBq/kg. Any areas of focally increased radiotracer uptake, at both the early and late PET scans, were considered as abnormal, despite the presence or absence of morphological changes of the CT scan. The normal distribution of the radiotracer was taken under consideration, which includes mainly the liver and the gallbladder, as it has hepatobiliary clearance rather than renal, the spleen, the pancreas, the submandibular, sublingual, lacrimal and parotid glands, the kidneys, the urinary bladder and the small intestine [22]. The maximum standardized uptake value (SUVmax) was calculated for each lesion.

A typical case of a 78 years man with PCa having PSA 7,3 ng/mL and also having Paget's disease was tested by the above procedure for initial staging. The ^{18}F -PSMA-1007 PET/CT imaging revealed diffusely increased radiotracer uptake in the bones of the pelvis with a SUVmax 9. The CT imaging of the pelvis was consistent with Paget's disease, with diffuse mixed osteosclerotic and osteolytic lesions, accompanied with bone expansion (Figure 1). The primary PCa was also revealed with focally increased radiotracer uptake in the left prostatic lobe with a SUVmax 19, as well as a second small focus of pathologically increased PSMA uptake in the right prostatic lobe with a SUVmax 23.

Another patient 79 years old, with PCa was studied with ^{18}F -choline PET/CT which showed diffuse bone metastasis in

the pelvis. He had PSA level, 412ng/mL. The ^{18}F -PSMA-1007 PET/CT imaging showed multiple foci of increased radiotracer uptake throughout the whole skeleton, including the skull, both humerus and femoral bones with indicative SUVmax 26 (Figure 2). Computed tomography showed rather similar BM. There were also lymph nodes metastases at the left internal mammary chain as well as the left inguinal areas, with a SUVmax 25.

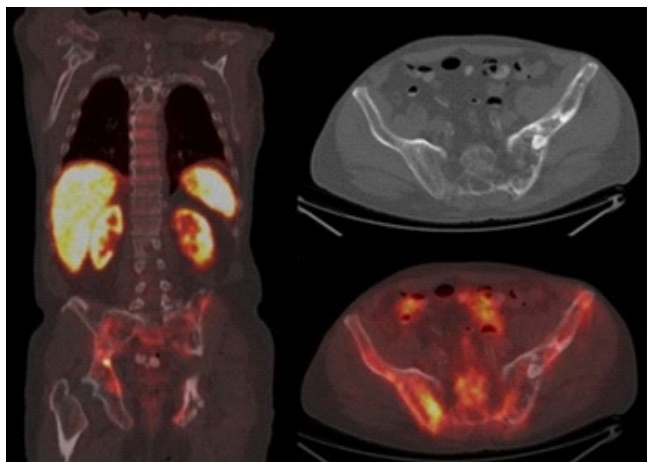


Figure 1. Coronal fused, axial CT and axial fused ^{18}F -PSMA PET/CT images demonstrating diffusely increased PSMA uptake in the bones of the pelvis, all findings consistent with Paget's disease.

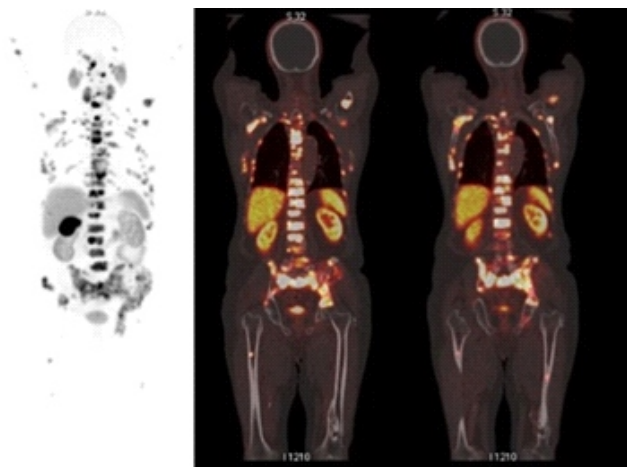


Figure 2. Maximum intensity projection (MIP) image and coronal fused ^{18}F -PSMA PET/CT images demonstrating multiple foci of increased radiotracer uptake throughout the whole skeleton, consistent to extensive metastatic bone disease.

The first case indicated that ^{18}F -PSMA PET/CT could easily differentiate PCa BM from Paget's disease, however benign conditions such as Paget's disease may also show PSMA uptake and the second case that ^{18}F -PSMA PET/CT scan was more sensitive than the ^{18}F -choline PET/CT scan, with high quality images. According to other authors the SUVmax value of BM in PCa was 16.57 ± 23.59 using the ^{18}F -PSMA PET/CT scan [23]. This imaging modality in accordance to other authors is better than ^{68}Ga -labelled PSMA-ligands and can better differentiate BM from healing fractures [24].

Very recently a novel PET radiopharmaceutical has been

approved both in USA and Europe: ^{18}F -fluciclovine (trans-1-amino-3- ^{18}F fluoro-cyclobutane carboxylic acid). Fluorine-18-fluciclovine is a synthetic amino acid that is transported by multiple sodium-dependent and sodium-independent channels found to be upregulated in PCa cells [25-27]. The main indication of use includes the detection and localization of PCa recurrence in patients with a rising PSA following prior therapy. The main advantages of ^{18}F -fluciclovine are the low urinary excretion, which allows for better evaluation of prostate bed and the low uptake in inflammatory cells (e.g. macrophages) [25-27]. There are no studies in the literature comparing ^{18}F -PSMA to ^{18}F -fluciclovine, however two studies comparing ^{18}F -fluciclovine to ^{68}Ga -PSMA, showed better performance for ^{68}Ga -PSMA in PCa patients with biochemical recurrence [28, 29].

So, ^{18}F -PSMA-1007 PET/CT imaging seems to be very promising in staging and restaging patients with PCa, especially when biochemical relapse is under consideration. Although it seems to perform better than other imaging modalities like bone scan, ^{18}F -FDG PET/CT or ^{18}F -choline PET/CT, its high cost and low availability must be considered. Further large studies need to be conducted in order to evaluate the accuracy and the predictive values of this method, emphasizing on bone metastases.

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