



PSMA PET/CT imaging and therapy

Prostate-specific membrane antigen (PSMA) is increasingly recognized as a novel target for the PET imaging of prostate cancer (PCa) and ^{68}Ga -DKFZ-11 (^{68}Ga -PSMA) has been suggested as a novel tracer for detection of PCa relapses and metastasis. First human studies of PSMA PET/CT imaging have demonstrated high tracer uptake at the sites of primary tumor and lymph node and bone metastasis in direct correlation with aggressiveness and Gleason scores. PSMA PET/CT seems to be a highly accurate imaging tool for restaging of prostate cancer patients with biochemical recurrence. PSMA PET/CT imaging may be used in order to develop a treatment strategy for recurrent disease even in patients with low PSA levels. As a theranostic approach its counterpart Lu-177 labelled ligands have a potential role for the treatment of castration resistant prostate cancer.

KEYWORDS: Prostate cancer; PSMA; PET/CT; biochemical recurrence; choline

Prostate cancer (Pca) is the most common solid cancer in men and prostate cancer is the second most common cause of death in developed countries [1]. Radical prostatectomy and radiation therapy are performed as primary therapy with a curative intent in patients with localized prostate cancer [2,3]. The selection of therapy in prostate cancer is mainly influenced by the presence or absence of metastasis. Studies with cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI), or functional imaging with F-18-FDG PET/CT and F-18-Choline PET/CT have shown disappointing sensitivity rates in detecting lymph node positive disease [4,5]. Pelvic lymph node dissection is considered as the gold standard for evaluating the presence of nodal involvement in patients with risk of nodal metastasis [6]. Currently there is no reliable imaging method for detecting lymph node metastasis.

Despite effective definitive therapy depending on the patient population studied, 15% to 40% of patients experience increasing PSA levels, which is called biochemical recurrence. European Association of Urology guidelines define biochemical recurrence as an increase of serum PSA value above 0.2 ng/ml and over 2 ng/ml above the nadir value after radiation therapy [2,3]. An accurate diagnosis of the site of prostate cancer recurrence is a key factor for treatment planning and patient management [3]. The selection of therapy in recurrent prostate cancer is mainly influenced by the presence or absence of metastasis, since salvage therapy is indicated in

localized recurrent disease and systemic therapy is indicated in metastatic disease. Studies with morphological imaging with CT and MRI, or functional imaging with F-18-FDG PET/CT and F-18-Choline PET/CT have shown disappointing sensitivity rates [7] and currently there is no reliable imaging method for detecting the site of disease in patients with biochemical recurrence [6-10]. Therefore, there is an absolute necessity for a diagnostic tool for precise localization of recurrences in asymptomatic patients with a rising prostate specific antigen (PSA) after definitive therapies, which could impact on management decisions [8-10].

Glutamate carboxypeptidase II, also known as prostate specific membrane antigen (PSMA) is a zinc dependent peptidase, highly expressed by all prostate cancers and its expression increases with tumor aggressiveness, metastatic disease and disease recurrence [11-13]. PSMA is also expressed in small intestine, renal tubules, salivary glands and tumor neovasculature [14]. PSMA is a type II membrane glycoprotein that has a short cytoplasmic tail, single intramembrane coil and a large extracellular part, which retains the enzymatic activity. Enzymatic activity of PSMA hydrolyzes the neuropeptide N-acetylaspartylglutamate (NAAG) that leads the production of glutamate and N-acetylaspartate. The amount of glutamate as a neurotransmitter is closely related with some neurologic diseases and many small molecule inhibitors of this enzymatic activity is developed based on phosphonates, thiols or ureas in order to treat some of neuropsychiatric diseases [15]. Binding of inhibitors or antibodies to the

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extracellular domain increases the internalization rate of PSMA, which constitutes the rationale of targeting for the delivery of radionuclides into the PSMA expressing cells.

The unique expression profile of PSMA provides an excellent target for prostate cancer imaging and therapy [16,17]. During last several years a number of small molecule PSMA enzyme inhibitors were labeled with radionuclides like I-123, I-131, Tc-99m, Ga-68 and Lu-177. Recently, Ga-68 labeled small molecule inhibitors Ga-68-DKFZ-11 (Glu-NH-CO-NH-Lys-(Ahx)-[Ga-68 (HBED-CC)] has been shown to be a novel radiotracer that show high cell uptake with prolonged cell surface retention resulted in a high tumor contrast. Relatively easy and efficient radiolabeling technique has led the compound to be a potential radiotracer that may detect prostate carcinoma relapses and metastasis by targeting the PSMA [17].

First human bio-distribution studies of PSMA PET/CT imaging have demonstrated intense radiotracer uptake in kidneys, salivary glands and urinary bladder due to excretion of radiotracer through kidneys [18,19] (FIGURE 1). High tracer uptake was observed at the sites of primary tumor, lymph and bone metastasis giving highest uptake at the sites of higher Gleason score. Afshar-Oromich *et al.* compared the positivity rate of PSMA PET/CT and F-18-choline PET/CT in 38 patients who have a

suspicion of recurrence [20]. The detection rate was significantly higher for PSMA PET/CT as compared to that of F-18-Choline PET/CT (86.5% vs. 70.3% respectively $p < 0.05$). When they analyzed the patients with low PSA levels this difference was more prominent in favor of PSMA, which also gave higher SUV max values than F-18-Choline. Giesel *et al.* compared the detection rate of PSMA PET/CT with 3D CT volumetric lymph node in patients with recurrent prostate cancer [21]. PSMA imaging was considered to be positive 31 lymph nodes in 7 patients and could be able to detect as small as 2.4 mm lymph nodes. On the other hand only 36% of these nodes were larger than 8 mm, which was a threshold for positivity in CT imaging. Afshar-Oromich *et al.* studied 42 patients and compared the positive lymph nodes in PSMA PET/CT with biopsy or surgery results and found out 100% specificity for pathological tracer uptake in lymph nodes [22]. The diagnostic sensitivity and specificity was found to be 76.6% and 100%, respectively. These findings are highly promising and it seems that PSMA imaging may have a potential role for the restaging of the disease. However, more prospective studies are needed in order to understand the exact role of PSMA imaging for staging purposes.

Afshar-Oromich *et al.* studied the diagnostic value of PSMA PET/CT in 318 patients with

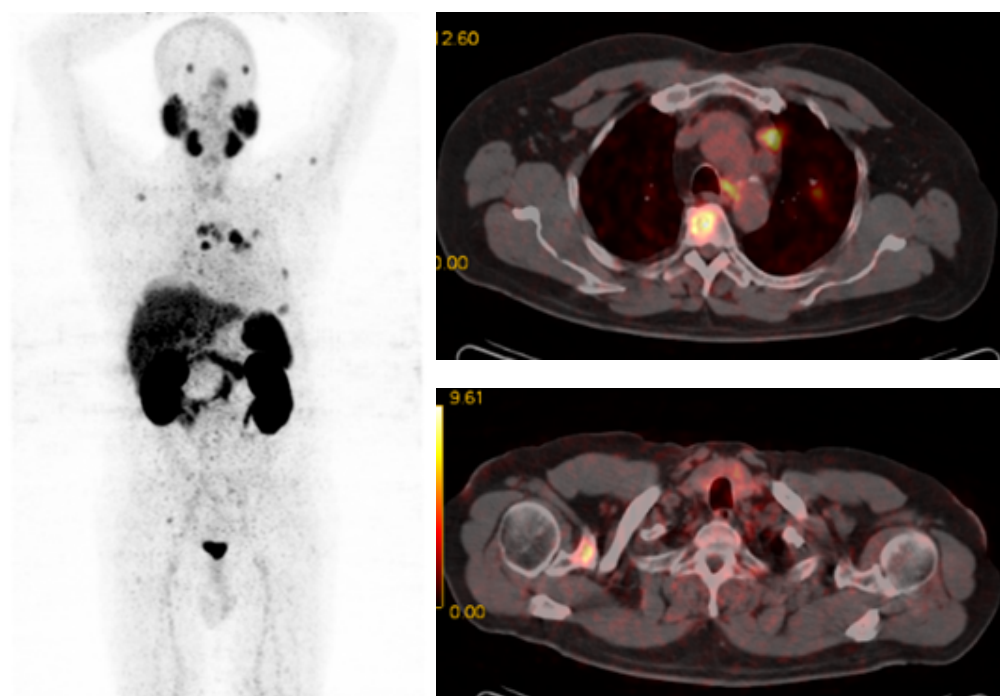


Figure 1. PSMA/PET/CT image of a patient who was treated with surgery and has a rising PSA, which was 0.9 ng/ml. Patient, has bone and mediastinal lymph node metastasis.

Table 1. Relation between positivity rates and the PSA in published papers so far.

	PSA level	Avg PSA	n	Positivity rate
	(2 - >2000)	4	155	80%
Verburg <i>et al.</i>	<1	N/A	27	44%
	1-2	N/A	19	79%
	>2 (2-2000)	N/A	109	89%
Afshar-Oromieh <i>et al.</i>	0.01-41395	161	311	82.8%
	<0,2	N/A	17	47.1%
	0.2-5	N/A	146	76.02%
Eiber <i>et al.</i>	0.2-59.4	4.78*	248	89.5%
	0.2-0.5	N/A	19	57.9%
	0.5-1	N/A	33	72.7%
	1-2	N/A	72	93%
	2-59.4	N/A	124	96.8%
Ceci <i>et al.</i>	0.2-32.2	3.5 ± 5.3	70	74.2%
	0.2-2	0, 81	36	55%

recurrent prostate cancer [22] (TABLE 1). The positivity rate was 82.2% in all-patient group. They reported high positive rates even in patients with low PSA values. The positivity rate was 47.1% and 64.3% in patients with PSA levels for <0.2 ng/ml and 0.2 to 2.0 ng/ml respectively. They reported that positivity rate was positively associated with PSA level and androgen deprivation therapy (ADT). Eiber *et al.* reported higher positivity rates in 258 patients with biochemical recurrence after radical prostatectomy [23]. They found that the positivity rates are closely associated with PSA levels and PSA velocity but not PSA doubling time. They reported a 57.9% positivity rate in patients with low PSA values (<0.5 ng/ml), which may considerably influence the management of the disease. Ceci *et al.* [24] and Verburg *et al.* [25] have studied the factors that may have an impact on the detection rate of PSMA PET/CT in patients with recurrent prostate cancer. Ceci *et al.* have reported a positivity rate of 74.2% in 70 patients and in a ROC analysis they found a cut off value of 6.5 months for PSA doubling time and 0.83 ng/ml for PSA value. So patients with low PSA levels and longer PSA doubling time may have a less likelihood to have a positive scan. Verburg *et al.* have reported a positivity rate of 44% in patients with PSA value of less than 1 ng/ml and they reported that positivity rate was positively associated with PSA level and PSA doubling time. Moreover, they showed these two parameters were independent determinants for finding M1 disease. These studies have shown that PET/CT imaging with a PCa targeted tracer, PSMA, seems to be a powerful tool and is superior to metabolic imaging

radiopharmaceuticals like FDG and Choline. All these preliminary results suggest PSMA PET/CT can be used effectively for restaging purposes in order to develop a treatment strategy even in patients with low PSA levels but to be confirmed with prospective studies.

Unique expression of PSMA and high sensitivity of the Ga-68 labelled ligands also provides as an excellent target for its counterpart Lu-177-PSMA-617 as a tool for radionuclide therapy in castration resistant prostate cancer. Cases who have benefit from this type of therapy have already reported [26]. It has been shown that parotid glands and kidneys are the target organs for toxicity [27]. However, dosimetry studies have shown that Lu-177-PSMA therapy is a safe method and cumulative activity of up to 30GBq can be given using kidneys as dose limiting organ. Currently many centers are applying Lu-177-PSMA therapy and we eagerly waiting for the clinical results.

In conclusion, PSMA PET/CT seems to be a highly accurate imaging tool for restaging of prostate cancer patients with biochemical recurrence. For accurate management of patients who developed biochemical recurrence, It is extremely important to differentiate local disease from systemic in order to develop a treatment strategy and to decide if the patient is a candidate for a salvage therapy or not. The sensitivity of anatomic imaging techniques like CT scan or MR imaging and the metabolic imaging techniques like bone scan, FDG PET/CT, F-18 NAF PET/CT or C-11 or F-18 labelled choline PET/CT imaging are far below then desired. PSMA PET/CT imaging may be used in order to develop a

treatment strategy even in patients with low PSA levels. As a theranostic approach its counterpart Lu-177 labelled ligands have a potential for the treatment of castration resistant prostate cancer.

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