PSMA PET/CT Imaging and Therapy

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Abstract

Prostate-specific membrane antigen (PSMA) is increasingly recognized as a novel target for the PET imaging of prostate cancer (PCa) and 68Ga-DKFZ-11 (68Ga-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

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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 neovascularature [14]. PSMA is a type II membrane glycoprotein that has a short cytoplasmic tail, single intra-membrane coil and a large extracellular part, which retains the enzymatic activity. Enzymatic activity of PSMA hydrolyzes the neuropeptide N-acetylasparglutarlate (NAAG) that leads the production of glutamate and N-acetylasparglutarlate. 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, thiol or ureas in order to treat some of neuropsychiatric diseases [15]. Binding of inhibitors or antibodies to the extracellular domain increases the internalization rate of PSMA, which constitutes the rational 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
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.
Table 1 Relation between positivity rates and the PSA in published papers so far.

<table>
<thead>
<tr>
<th>PSA level</th>
<th>Avg PSA</th>
<th>n</th>
<th>Positivity rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2 &gt; 2000)</td>
<td>4</td>
<td>155</td>
<td>80%</td>
</tr>
<tr>
<td>Verburg et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>N/A</td>
<td>27</td>
<td>44%</td>
</tr>
<tr>
<td>1-2</td>
<td>N/A</td>
<td>19</td>
<td>79%</td>
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<tr>
<td>&gt;2</td>
<td>N/A</td>
<td>109</td>
<td>89%</td>
</tr>
<tr>
<td>Afshar-Oromieh et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01-41395</td>
<td>161</td>
<td>311</td>
<td>82.8%</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>N/A</td>
<td>17</td>
<td>47.1%</td>
</tr>
<tr>
<td>0.2-5</td>
<td>N/A</td>
<td>146</td>
<td>76.02%</td>
</tr>
<tr>
<td>0.2-59.4</td>
<td>4.78*</td>
<td>248</td>
<td>89.5%</td>
</tr>
<tr>
<td>Eiber et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>N/A</td>
<td>19</td>
<td>57.9%</td>
</tr>
<tr>
<td>0.5-1</td>
<td>N/A</td>
<td>33</td>
<td>72.7%</td>
</tr>
<tr>
<td>1-2</td>
<td>N/A</td>
<td>72</td>
<td>93%</td>
</tr>
<tr>
<td>Ceci et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-59.4</td>
<td>N/A</td>
<td>124</td>
<td>96.8%</td>
</tr>
<tr>
<td>0.2-32.2</td>
<td>3.5 ± 5.3</td>
<td>70</td>
<td>74.2%</td>
</tr>
<tr>
<td>0.2-2</td>
<td>0.81</td>
<td>36</td>
<td>55%</td>
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</tbody>
</table>

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.
References


