Eur J Nucl Med Mol Imaging (2013) 40:969–970
DOI 10.1007/s00259-013-2385-z

LETTER TO THE EDITOR

Comment on Afshar-Oromieh et al.: PET imaging with a [^{68}Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions

Sven Norbert Reske · Gordon Winter · Benjamin Baur · Hans-Jürgen Machulla · Thomas Kull

Received: 30 January 2013 / Accepted: 26 February 2013 / Published online: 5 April 2013

Dear Sir,

It was with particular interest that we read the article by Afshar-Oromieh et al. [1]. The authors developed a novel ^{68}Ga-labelled prostate-specific membrane antigen (PSMA)-binding small molecule, combining the well-known urea-based inhibitory motif glutamate-urea-lysine [2] with the lipophilic *N,N′*-bis[2-hydroxy-5-(carboxyethyl)-benzyl] ethylenediamine-*N,N′*-diacetic acid (HBED-CC) chelator for ^{68}Ga [3]. The authors reasoned that the lipophilicity of HBED-CC might improve binding to PSMA and thus enable positron emission tomography (PET)/CT imaging of prostate carcinoma (PCa) [3]. Recognizing that PSMA targeting is one of the most exciting topics of molecular imaging and targeted therapy in prostate cancer at present, the authors are to be congratulated on offering the first larger patient series of 37 individuals with relapsing PCa, examined with a ^{68}Ga-labelled PSMA inhibitor and PET/CT. Examination of the biodistribution of the novel tracer and capability to show presumed sites of metastatic involvement were major intents of the study. The authors described excellent lesion detection with impressive contrast of presumed sites of metastatic deposits of prostate cancer in 31 of their 37 patients (83.8 %) [1].

A detailed discussion of the many clinical and technical ambiguous aspects of the study is beyond the scope of this letter. However, we think that in a study comprising 37 patients a discussion of 42 patients in the text needs clarification. In addition, we cannot follow the assumption that a prostate involved with prostate cancer and treated with local radiation therapy and androgen deprivation therapy can be regarded as a ‘normal prostate’. Also, interpretation of the clinical state of patient 21 described in the legend of Fig. 7 as harbouring probably dedifferentiated prostate cancer because of positive pelvic nodes and a serum prostate-specific antigen (PSA) concentration of 0.01 ng/ml is confusing as this patient already had a Gleason score of 9 of his primary and bone as well as soft tissue metastases (Table 1) and therapy beyond prostatectomy is not discussed. Moreover, one of the two positive nodes in this patient is an inguinal node, a localization where positive nodes from PCa are very rare. Generally, a definition of assessment criteria of assumed prostate cancer deposits and verification by some reference standard in more than the six histologically controlled patients described would have been very welcome. Interestingly, the authors try to explain ^{68}Ga-PSMA inhibitor biodistribution with rather high tracer uptake in lacrimal and salivary glands, nasal mucosa, liver, spleen, bowel, kidneys and bladder in the context of known PSMA tissue expression. A very similar biodistribution to that described by the authors was observed in a series of seven patients, examined with the PSMA inhibitor MIP-1072 ([(*S*)-2-(3-((*S*)-1-carboxy-5-(4-iodobenzylamino)pentyl) ureido) pentanedioic acid) and MIP-1095 ([(*S*)-2-(3-((*S*)-1-carboxy-5-(3-(4-iodophenyl)pentyl)ureido) pentanedioic acid) by Barrett et al. very recently [4]. Also in this study, lesions from PCa could be imaged with high contrast using single photon emission computed tomography (SPECT)/CT as the imaging technique [4]. Studying relapsing prostate cancer with another ^{68}Ga-PSMA inhibitor, ^{68}Ga-DOTA-DUPA-

An author’s reply to this comment is available at doi:10.1007/s00259-013-2386-y.

S. N. Reske (✉) · G. Winter · B. Baur · H.-J. Machulla · T. Kull
Klinik für Nuklearmedizin, Universität Ulm, Ulm, Germany
e-mail: sven.reske@uniklinik-ulm.de

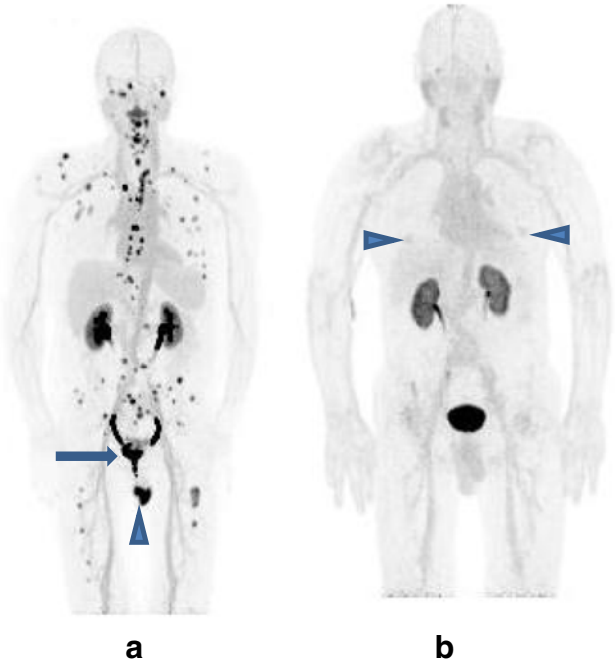

Fig. 1 **a** A 70-year-old patient with a history of prostatectomy because of PCa 12 years before the examination, Gleason score 5+5, local radiation therapy and castration-resistant PCa at presentation, PSA 3 ng/ml. ^{11}C-choline PET/CT showed large local recurrence and disseminated bone marrow metastases. Completely concordant ^{68}Ga-DOTA-DUPA-Pep findings with disseminated bone marrow metastases confirmed by MRI and a large local recurrence (*arrow*). *Note* normal tissue background mostly in blood pool, uptake in kidneys and urinary tract with some urine contamination (*arrowhead*) due to urinary conduit because of incontinence and very faint uptake in salivary glands. Maximum intensity projection (MIP) of a PET image of the trunk acquired 1 h after injection of 85 MBq ^{68}Ga-DOTA-DUPA-Pep. **b** A 74-year-old patient with a history of PCa 2 years before the examination, stage II, Gleason score 3+3, androgen deprivation therapy with bicalutamide, PSA at presentation 0.2 ng/ml. ^{68}Ga-DOTA-DUPA-Pep PET shows uptake in kidneys, urinary tract and blood pool and faintly in salivary and lacrimal glands. There is no evidence of tumour deposits. Interestingly, also faint uptake is seen due to gynaecomastia (*arrowheads*). MIP PET as in **a**, 105 MBq ^{68}Ga-DOTA-DUPA-Pep

Pep (8,11-dibenzyl-2,7,10,13,22,27-hexaoxo-1-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraaza-cyclododecan-1-yl)-3,6,9,12,21,26,28-heptaazahentriacontane-25,29,31-tricarboxylic acid) we can confirm the very favourable imaging properties of PSMA targeting with urea-based inhibitors for showing metastatic disease with PET/CT (Fig. 1a), but we observed a remarkably different biodistribution (Fig. 1b) to that described by Afshar-Oromieh et al. [5]. We found predominant tracer uptake in kidneys, urinary tract, blood pool and lesions from PCa (Fig. 1a) and only very faint uptake in salivary glands and also in gynaecomastia (Fig. 1b). Interestingly, a current paper by Pomper's group using the ^{18}F-labelled PSMA inhibitor *N*-[*N*-[(*S*)-1,3-dicarboxypropyl] carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine (^{18}F-DCFBC) described a strikingly similar biodistribution to that of ^{68}Ga-DOTA-DUPA-Pep [6]. Thus, PSMA addressing through urea-based inhibitors with appropriate radiolabelled peptides seems to provide a very promising approach for targeting various stages of PCa in patients; however, factors governing extraprostatic tissue distribution need further careful analysis and consideration.

References

1. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a [(68)Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging 2013;40:486–95. doi: 10.1007/s00259-012-2298-2
2. Bařinka C, Rojas C, Slusher B, Pomper M. Glutamate carboxypeptidase II in diagnosis and treatment of neurologic disorders and prostate cancer. Curr Med Chem 2012;19:856–70.
3. Eder M, Schäfer M, Bauder-Wüst U, Hull WE, Wängler C, Mier W, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem 2012;23:688–97.
4. Barrett JA, Coleman RE, Goldsmith SJ, Vallabhajosula S, Petry NA, Cho S, et al. First-in-man evaluation of 2 high-affinity PSMA-avid small molecules for imaging prostate cancer. J Nucl Med 2013;54:380–7.
5. Winter G, Zlatopolskiy B, Kull T, Bertram J, Genze F, Cudek G, et al. 68Ga-DOTA-DUPA-Pep as a new peptide conjugate for molecular imaging of prostate carcinoma. J Nucl Med 2011;52(Suppl 1):1597.
6. Cho SY, Gage KL, Mease RC, Senthamizhchelvan S, Holt DP, Jeffrey-Kwanisai A, et al. Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. J Nucl Med 2012;53:1883–91.