Eur J Nucl Med Mol Imaging (2016) 43:394–396
DOI 10.1007/s00259-015-3212-5

EDITORIAL COMMENTARY

^{68}Ga-PSMA-HBED-CC PET/CT: where molecular imaging has an edge over morphological imaging

Felix M. Mottaghy[1,2] · **Florian F. Behrendt**[1] · **Frederik A. Verburg**[1,2]

Published online: 10 October 2015

Nuclear medicine is currently taking great steps towards gaining a much more prominent role in the care of patients with prostate cancer. Prostate-specific membrane antigen (PSMA) has been a theranostic target of interest in prostate cancer for over two decades and ^{111}In/^{177}Lu antibody-based imaging and therapy have been studied extensively but without gaining widespread clinical acceptance [1–3]. However, since the introduction of novel functional ligands for PSMA such as Glu-urea-Lys-(Ahx)-[^{68}Ga(HBED-CC)] (^{68}Ga-PSMA) [4, 5], PSMA-DKFZ-617 [6–8] or EuK-Subkff-^{68}Ga-DOTAGA [9], the number of publications on specifically PSMA-targeted imaging has increased exponentially. This shows the extraordinary potential of this approach as a blockbuster modality for nuclear medicine.

^{68}Ga-PSMA PET/CT is a fine example of theranostic nuclear medicine. The tracer ^{68}Ga-PSMA is eminently suitable for selection of patients who can be treated with the novel ^{177}Lu-labelled therapeutic tracer PSMA-DKFZ-617 [6]. Dramatic success has already been observed even in the small initial number of patients with extensively metastasized therapy-refractory prostate cancer metastases treated with this tracer once strong tracer uptake had been established in prior diagnostic ^{68}Ga-PSMA PET/CT [6, 10]. Therapeutic nuclear medicine therefore now has a truly large new potential patient collective in whom molecular targeted endogenous radiotherapy may play a pivotal role. Furthermore, PSMA is not only expressed strongly by prostate cancer cells, but also in a variety of other normal tissues and solid tumours – mainly in the tumour vasculature [11–18]. This might open the door to nuclear medicine making the long-sought-after inroad into non-thyroid, non-neuroendocrine cancer therapy even though a sustainable multicentre effort has to be initiated to realize this potential.

In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Giesel et al. report a study comparing the performance of ^{68}Ga-PSMA PET and conventional morphological imaging with CT in 21 patients scanned prior to radiation therapy [19]. Their findings (again) show the strong potential of ^{68}Ga-PSMA PET/CT. With conventional morphological criteria based on the size of lymph nodes only 22 % of PET-positive lesions were identified as suspicious for malignancy, and only 7 of 14 patients (50 %) identified as having lymph node metastases on PET were also identified as such using CT-based lymph node diameter measurements. Previous studies have shown the high signal-to-background ratio typical of ^{68}Ga-PSMA PET/CT [18, 20, 21], Giesel et al. now provide further detail on the diagnostic power of this novel imaging modality: the smallest PET-positive lesions had a short-axis diameter of only 2.4 mm. This is hardly greater than the annihilation distance in water for ^{68}Ga-emitted positrons of 1.7 mm, and thus approaches the lower limit of the physically possible resolution in human PET imaging.

It is exactly the setting of patients referred for salvage radiation therapy in which ^{68}Ga-PSMA PET/CT may prove to be of great value. Currently standard treatment for postoperative elevation of prostate-specific antigen (PSA) levels is radiation therapy of the former prostate region. It is recommended that this therapy is best initiated at PSA levels ≤0.5 ng/ml [22]. It has already been shown that even at such low levels

This Editorial Commentary refers to the article http://dx.doi.org/10.1007/s00259-015-3106-6.

✉ Felix M. Mottaghy
fmottaghy@ukaachen.de

[1] Department of Nuclear Medicine, RWTH University Hospital Aachen, Pauwelsstraße 30, 52074 Aachen, Germany

[2] Department of Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

^{68}Ga-PSMA PET/CT is able to show pathological accumulation outside the prostate bed, mostly in pelvic lymph node metastases, in approximately half of patients with a positive PET/CT scan, thus affecting treatment in approximately a quarter of all patients referred for ^{68}Ga-PSMA PET/CT with such low PSA levels [4, 23]. Here ^{68}Ga-PSMA PET/CT will markedly influence treatment because it allows either avoidance of a non-effective radiation treatment with considerable potential side effects or modification of treatment by inclusion of the affected lymph nodes in the radiation field.

While CT imaging has its place in staging of prostate cancer, MRI, especially using multiparametric imaging including diffusion-weighed sequences, is the more sensitive morphological imaging method. Although choline, the de-facto standard nuclear medicine tracer for prostate cancer, labelled with either ^{18}F or ^{11}C, has been proven to be marginally better than diffusion-weighed MRI [24, 25], neither modality has so far achieved optimal sensitivity and specificity for clinical use. Direct comparison of ^{68}Ga-PSMA PET imaging and multiparametric MRI would be of great interest for nuclear medicine, even though, as already indicated in initial studies, the best option for the future will probably consist of hybrid PET/MRI imaging rather than either modality alone [27, 27].

Still, with all these promising new developments and the great diagnostic and therapeutic potential currently being unlocked by what seems almost an avalanche of studies into ^{68}Ga-PSMA PET/CT, we all need to treat the current situation with a high degree of alertness. Recent history of nuclear medicine is awash with examples of what can happen if nuclear medicine as a discipline remains fractured and will not close ranks for a unified effort to gain acceptance in mainstream medicine.

Currently a number of different competing and only marginally differing radiolabelled functional PSMA ligands are being investigated, and the preferences in the use of these experimental tracers among the nuclear medicine communities in those countries where the use of such tracers is relatively less restrictive appear to be becoming increasingly divergent. Furthermore, all research effort has so far been spearheaded by academic institutions which do not have either the financial and organizational power or the commercial incentive that a strong commercial partner might have to undertake the entire study process necessary for regulatory approval. Without such approval, many countries will not even allow the use of ^{68}Ga-PSMA PET/CT, regardless of how good the tracer may appear in the initial studies being published now. A dire example of where this may lead is the situation with somatostatin receptor-targeted imaging and therapy. ^{68}Ga-labelled somatostatin analogues have been reported for well over a decade now [28–32]. However, the multitude of available analogues and lack of a commercially interested industrial party has led to the situation where ^{111}In-pentetreotide [33], which is clearly inferior in terms of both diagnostic performance and patients' radiation exposure [34], remains the only registered radiopharmaceutical. This in turn means that in many countries the latter compound remains the only compound allowed for the practice or reimbursement of somatostatin-receptor targeted imaging.

We therefore call upon the nuclear medicine community not to waste this unique opportunity to greatly enlarge the role of nuclear medicine by the practice of the same petty rivalry that in the past could be seen so often. Instead we should confer and put in a strong united effort to quickly gain mainstream acceptance of targeted imaging and therapy with a functional PSMA ligand by performing proper prospective multicentre studies. We strongly believe that with such a concerted action in the end none will come to harm and all will benefit. We have a magic bullet in our hands and should be careful not to lose it.

Compliance with ethical standards

Conflicts of interest F.M.M. and F.F.B. have received grant support and speakers' fees from Bayer Healthcare. F.A.V. is a consultant to Bayer Healthcare.

References

1. Tagawa ST, Milowsky MI, Morris M, Vallabhajosula S, Christos P, Akhtar NH, et al. Phase II study of lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res. 2013;19:5182–91.
2. Franc BL, Cho SY, Rosenthal SA, Cui Y, Tsui B, Vandewalker KM, et al. Detection and localization of carcinoma within the prostate using high resolution transrectal gamma imaging (TRGI) of monoclonal antibody directed at prostate specific membrane antigen (PSMA) – proof of concept and initial imaging results. Eur J Radiol. 2013;82:1877–84.
3. Rosenthal SA, Haseman MK, Polascik TJ. Utility of capromab pendetide (ProstaScint) imaging in the management of prostate cancer. Tech Urol. 2001;7:27–37.
4. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42:197–209.
5. Eder M, Neels O, Muller M, Bauder-Wust U, Remde Y, Schafer M, et al. Novel preclinical and radiopharmaceutical aspects of [68Ga]Ga-PSMA-HBED-CC: a new PET tracer for imaging of prostate cancer. Pharm (Basel). 2014;7:779–96.
6. Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benesova M, Mier W, et al. [177Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42:987–8.
7. Afshar-Oromieh A, Hetzheim H, Kratochwil C, Benesova M, Eder M, Neels OC, et al. The novel theranostic PSMA-ligand PSMA-617 in the diagnosis of prostate cancer by PET/CT: biodistribution in humans, radiation dosimetry and first evaluation of tumor lesions. J Nucl Med. 2015. doi:10.2967/jnumed.115.161299

8. Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for 177Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015. doi:10.1007/s00259-015-3174-7
9. Herrmann K, Bluemel C, Weineisen M, Schottelius M, Wester HJ, Czernin J, et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. J Nucl Med. 2015;56:855–61.
10. Ahmadzadehfar H, Rahbar K, Kurpig S, Bogemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. EJNMMI Res. 2015;5:114.
11. Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS, Gaudin PB. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res. 1999;59:3192–8.
12. Haffner MC, Laimer J, Chaux A, Schafer G, Obrist P, Brunner A, et al. High expression of prostate-specific membrane antigen in the tumor-associated neo-vasculature is associated with worse prognosis in squamous cell carcinoma of the oral cavity. Mod Pathol. 2012;25:1079–85.
13. Haffner MC, Kronberger IE, Ross JS, Sheehan CE, Zitt M, Muhlmann G, et al. Prostate-specific membrane antigen expression in the neovasculature of gastric and colorectal cancers. Hum Pathol. 2009;40:1754–61.
14. Mhawech-Fauceglia P, Smiraglia DJ, Bshara W, Andrews C, Schwaller J, South S, et al. Prostate-specific membrane antigen expression is a potential prognostic marker in endometrial adenocarcinoma. Cancer Epidemiol Biomarkers Prev. 2008;17:571–7.
15. Samplaski MK, Heston W, Elson P, Magi-Galluzzi C, Hansel DE. Folate hydrolase (prostate-specific membrane [corrected] antigen) 1 expression in bladder cancer subtypes and associated tumor neovasculature. Mod Pathol. 2011;24:1521–9.
16. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3:81–5.
17. Verburg FA, Krohn T, Heinzel A, Mottaghy FM, Behrendt FF. First evidence of PSMA expression in differentiated thyroid cancer using [(68)Ga]PSMA-HBED-CC PET/CT. Eur J Nucl Med Mol Imaging. 2015;42:1622–3.
18. Krohn T, Verburg FA, Pufe T, Neuhuber W, Vogg A, Heinzel A, et al. [(68)Ga]PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. Eur J Nucl Med Mol Imaging. 2015;42:210–4.
19. Giesel FL, Fiedler H, Stefanova M, Sterzing F, Rius M, Kopka K, et al. PSMA PET/CT with Glu-urea-Lys-(Ahx)-[Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015. doi:10.1007/s00259-015-3106-6
20. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014;41:11–20.
21. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a [68Ga]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.
22. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467–79.
23. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med. 2015;56:668–74.
24. Souvatzoglou M, Eiber M, Takei T, Furst S, Maurer T, Gaertner F, et al. Comparison of integrated whole-body [11C]choline PET/MR with PET/CT in patients with prostate cancer. Eur J Nucl Med Mol Imaging. 2013;40:1486–99.
25. Yamaguchi T, Lee J, Uemura H, Sasaki T, Takahashi N, Oka T, et al. Prostate cancer: a comparative study of 11C-choline PET and MR imaging combined with proton MR spectroscopy. Eur J Nucl Med Mol Imaging. 2005;32:742–8.
26. Afshar-Oromieh A, Haberkorn U, Hadaschik B, Habl G, Eder M, Eisenhut M, et al. PET/MRI with a 68Ga-PSMA ligand for the detection of prostate cancer. Eur J Nucl Med Mol Imaging. 2013;40:1629–30.
27. Picchio M, Mapelli P, Panebianco V, Castellucci P, Incerti E, Briganti A, et al. Imaging biomarkers in prostate cancer: role of PET/CT and MRI. Eur J Nucl Med Mol Imaging. 2015;42:644–55.
28. Cremonesi M, Ferrari M, Zoboli S, Chinol M, Stabin MG, Orsi F, et al. Biokinetics and dosimetry in patients administered with (111)In-DOTA-Tyr(3)-octreotide: implications for internal radiotherapy with (90)Y-DOTATOC. Eur J Nucl Med. 1999;26:877–86.
29. Hofmann M, Maecke H, Börner AR, Weckesser E, Schöffski P, Oei ML, et al. Biokinetics and imaging with the somatostatin receptor PET radioligand 68Ga-DOTATOC: preliminary data. Eur J Nucl Med. 2001;28:1751–7.
30. Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging. 2008;35:1847–56.
31. Forrer F, Uusijarvi H, Waldherr C, Cremonesi M, Bernhardt P, Mueller-Brand J, et al. A comparison of (111)In-DOTATOC and (111)In-DOTATATE: biodistribution and dosimetry in the same patients with metastatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2004;31:1257–62.
32. Wild D, Macke HR, Waser B, Reubi JC, Ginj M, Rasch H, et al. 68Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5. Eur J Nucl Med Mol Imaging. 2005;32:724.
33. Joseph K, Stapp J, Reinecke J, Skamel HJ, Hoffken H, Neuhaus C, et al. Receptor scintigraphy with 111In-pentetreotide for endocrine gastroenteropancreatic tumors. Horm Metab Res Suppl. 1993;27:28–35.
34. Buchmann I, Henze M, Engelbrecht S, Eisenhut M, Runz A, Schafer M, et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2007;34:1617–26.