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EDITORIAL

Al^{18}F-NOTA-octreotide and ^{18}F-SiFA*lin*-TATE: two 'new kids on the block' in somatostatin receptor imaging

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Since their introduction in clinical routine, somatostatin receptor agonists (SSAs) labelled with the positron-emitting radionuclide gallium-68, collectively referred to as ^{68}Ga-DOTA-peptides, have gradually replaced the use of ^{111}In-DTPA-octreotide for imaging of the somatostatin receptor (SSTR) in patients with neuro-endocrine tumours (NETs). Apart from the specific advantages of PET over SPECT, such as a higher sensitivity (counts/Bq) and spatial resolution, the higher affinity of ^{68}Ga-DOTA-peptides for the SSTR-subtype 2, which is the most overexpressed SSTR-subtype in NETs, offers an additional benefit in detecting SSTR-expressing lesions. Indeed, superior performance of ^{68}Ga-DOTA-peptide-PET was demonstrated by several groups when comparing it head-to-head to ^{111}In-DTPA-octreotide-SPECT in patients with NETs, with mainly a significantly higher sensitivity in detecting SSTR-overexpressing lesions [1–4].

Although PET-imaging of NETs with ^{68}Ga-DOTA-peptides is a well-established and validated technique and offers the additional advantage of forming a theranostic twin with ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC, which are currently the most frequently used radiopharmaceuticals for peptide receptor radionuclide therapy (PRRT) in these patients, the use of gallium-68 as a radionuclide also has several disadvantages, mainly of logistic nature. Gallium-68 has the theoretical advantage that it can be made available in nuclear medicine departments from a ^{68}Ge/^{68}Ga-generator, thus not requiring a cyclotron. While in the first years, ^{68}Ge/^{68}Ga-generators were mainly found in larger nuclear medicine departments with access to a dedicated radiopharmacy staff that was needed for tracer production, the introduction and very rapid clinical implementation of ^{68}Ga-PSMA-11 (^{68}Ga-HBED-CC) for imaging of patients with prostate cancer since 2014, has made ^{68}Ge/^{68}Ga-generators and production facilities more widely present. Furthermore, newer generation ^{68}Ge/^{68}Ga-generators have received regulatory approval and kit-based labelling approaches to produce ^{68}Ga-DOTA-peptides, such as SomaKit TOC™ (Advanced Accelerator Applications S.A.) and NETSPOT® (Advanced Accelerator Applications USA), have become available upon approval by the European Medicines Agency and the Food and Drug Administration, respectively. Despite these advances, the overall activity yield per production batch of ^{68}Ga-labelled compound remains low (capacity of two to four patients per production) and the half-life of gallium-68 is relatively short (68 min), limiting the potential for centralized production and distribution. In the future, some possibilities may be opened up in this field by advances in the cyclotron production of gallium-68. Apart from logistic disadvantages, gallium-68 also has drawbacks based on its physical characteristics, being its relatively high positron energy (E_{mean} = 0.83 MeV) and thus relatively long positron range (R_{mean} = 3.5 mm), which may result in a sub-optimal spatial resolution [5]. For these reasons, the possibilities of using other PET-radionuclides for SSTR imaging should be explored.

Among positron-emitting radionuclides, fluorine-18 is the most commonly used radionuclide for clinical PET imaging and offers several advantages over gallium-68: (1) logistic advantages: fluorine-18 can be produced by cyclotrons in large amounts and its longer half-life of 109.8 min allows fluorine-18-labelled tracers to be transported to remote hospitals that do not have a cyclotron on site; (2) physical properties: fluorine-18 has a low positron energy (E_{mean} = 0.25 MeV) and therefore shorter positron range (R_{mean} = 0.6 mm), offering higher intrinsic spatial resolution [5].

Similarly to PET imaging of prostate specific membrane antigen (PSMA) in prostate cancer, where ^{18}F-labelled compounds, such as ^{18}F-PSMA-1007 [6, 7], have been developed

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to accommodate for the high tracer demand in this field, also in PET imaging of SSTRs, development of ^{18}F-labelled compounds has been successful. Already in 2006, Meisetschläger et al. evaluated a fluorine-18 labelled SSA, Gluc-Lys-[^{18}F]FP-TOCA, in 25 patients with SSTR-positive tumours seen on ^{111}In-DTPA-octreotide scan and performed a direct comparison in 16 of these patients [8]. Despite the absence of trapping after cellular internalization of this ^{18}F-labelled compound, a visual image analysis revealed a significantly higher number of lesions (factor of 2.4) and an improved interobserver correlation for PET. A time-consuming multistep synthesis of this tracer with limited radiochemical yield has however hampered its implementation in routine clinical practice [8, 9]. More recently, ^{18}F-FET-βAG-TOCA showed a favourable safety, imaging and dosimetric profile when evaluated for SSTR-PET-imaging in 9 patients with NETs [10] with high tumour-to-background ratios, resulting in images with excellent contrast. Larger clinical trials for this promising tracer, including a direct comparison with ^{68}Ga-DOTATATE-PET/CT, are currently ongoing [9, 10].

In this issue of EJNMMI, two image-of-the month papers demonstrate the high potential of ^{18}F-labelled compounds for PET imaging of SSTRs. In a first image-of-the-month paper, Pauwels et al. show a first comparison between Al^{18}F-NOTA-octreotide-PET and ^{68}Ga-DOTATATE-PET in a patient with diffuse metastases of a rectal NET [5]. They demonstrate comparable uptake patterns for both tracers with diffuse liver metastases and several bone and lymph node metastases, but higher uptake values and tumour-to-background ratios as well as improved contrast in smaller lesions using Al^{18}F-NOTA-octreotide. In tracer production, the Al^{18}F-labelling method developed by McBride et al. combines the advantages of a chelator-based radiolabelling method with the unique properties of the radionuclide of choice, in this case fluorine-18 [11]. Al^{18}F-NOTA-octreotide was developed by Laverman et al. and has been compared to ^{111}In-DTPA-octreotide and ^{68}Ga-NOTA-octreotide in preclinical models [12, 13], demonstrating high in vitro binding affinity to SSTR. Very recently, Long et al. reported their first clinical experience with Al^{18}F-NOTA-octreotide in 3 healthy volunteers and 22 NET patients [14]. The tracer was shown to be safe with a favourable dosimetry and biodistribution profile, providing excellent detection of tumoural lesions with high tumour-to-background ratios. The patient presented by Pauwels et al. is part of a prospective phase 1 clinical study evaluating the potential of Al^{18}F-NOTA-octreotide as a SSTR-PET-imaging agent in patients with NETs, in comparison to routine clinical ^{68}Ga-DOTA-peptide-PET (NCT03883776).

In a second image-of-the-month paper, Ilhan et al. show their first-in-human PET/CT images using ^{18}F-SiFA*lin*-TATE in a patient with a metastatic NET, in comparison to ^{68}Ga-DOTATOC [5]. They also found that the uptake pattern in cardiac and bone metastases as well as the uptake in healthy tissue is highly comparable between both tracers, with higher uptake values using ^{18}F-SiFA*lin*-TATE in the majority of the lesions. ^{18}F-SiFA*lin*-TATE can be produced by taking advantage of thermodynamically favoured formation of silicon-^{18}F bonds (silicon-fluoride acceptor (SiFA) chemistry) [15] and radiolabelling of SiFA is exceptionally mild, proceeds without forming side products and can be performed by even untrained personnel [16]. In in vivo biodistribution studies in AR42J tumour-bearing mice, ^{18}F-SiFA*lin*-TATE showed comparable pharmacokinetic properties as ^{68}Ga-DOTATATE, displaying a high and specific tumour uptake and low non-target organ accumulations [15]. Also in comparative small-animal PET/CT-imaging of SSTR-positive tumour-bearing mice, ^{18}F-SiFA*lin*-TATE and ^{68}Ga-DOTATATE displayed similar uptake patterns in tumours, with higher uptake values using ^{18}F-SiFA*lin*-TATE [15]. Together with this preclinical data, the first-in-human ^{18}F-SiFA*lin*-TATE-PET/CT images support its use for SSTR-imaging and potential PRRT evaluation in NET patients and warrant further studies to evaluate it as a diagnostic tool.

Apart from fluorine-18, other positron-emitting radionuclides, such as copper-64, have been evaluated for SSTR-PET-imaging. Copper-64 has the advantage of a longer half-life (12.7 h), and thus, as fluorine-18, the theoretical possibility of centralized production and distribution. However, copper-64 has relatively limited applications and a limited synthesis capacity at the moment. Regarding SSTR-PET-imaging, Pfeifer et al. found a significantly higher diagnostic sensitivity and accuracy of ^{64}Cu-DOTATATE-PET compared to ^{111}In-DTPA-octreotide-SPECT in 112 patients with NETs, with more lesions being detected on ^{64}Cu-DOTATATE-PET in 75 % of patients, twice as many lesions detected on ^{64}Cu-DOTATATE-PET in total and lesions detected in organs not identified as disease-involved by ^{111}In-DTPA-octreotide-SPECT in 36 % of patients [17]. As ^{68}Ga-DOTATATE, ^{64}Cu-DOTATATE has the advantage of forming a theranostic twin with ^{177}Lu-DOTATATE.

In conclusion, the evolution towards ^{18}F-labelled tracers for imaging of SSTR-expressing tumours overcomes a number of important hurdles of ^{68}Ga-DOTA-peptides and potentially makes SSTR-PET-imaging more widely available. Further studies are, however, needed to evaluate these tracers not only as diagnostic tools but also as prognostic tools and as tools for assessing eligibility to PRRT.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

Ethical approval This article does not describe any studies with human participants or animals performed by the author.

References

1. Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med. 2007;48:508–18.
2. Deppen SA, Liu E, Blume JD, Clanton J, Shi C, Jones-Jackson LB, et al. Safety and efficacy of 68Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. J Nucl Med. 2016;57:708–14.
3. Sadowski SM, Neychev V, Millo C, Shih J, Nilubol N, Herscovitch P, et al. Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. J Clin Oncol. 2016;34:588–96.
4. Van Binnebeek S, Vanbilloen B, Baete K, Terwinghe C, Koole M, Mottaghy FM, et al. Comparison of diagnostic accuracy of 111In-pentetreotide SPECT and 68Ga-DOTATOC PET/CT: a lesion-by-lesion analysis in patients with metastatic neuroendocrine tumours. Eur Radiol. 2016;26:900–9.
5. Conti M, Eriksson L. Physics of pure and non-pure positron emitters for PET: a review and a discussion. EJNMMI Phys. 2016;3:8.
6. Giesel FL, Knorr K, Spohn F, Will L, Maurer T, Flechsig P, et al. Detection efficacy of (18)F-PSMA-1007 PET/CT in 251 patients with biochemical recurrence of prostate cancer after radical prostatectomy. J Nucl Med. 2019;60:362–8.
7. Rauscher I, Kronke M, Konig M, Gafita A, Maurer T, Horn T, et al. Matched-pair comparison of (68)Ga-PSMA-11 and (18)F-PSMA-1007 PET/CT: frequency of pitfalls and detection efficacy in biochemical recurrence after radical prostatectomy. J Nucl Med. 2019. https://doi.org/10.2967/jnumed.119.229187.
8. Meisetschlaeger G, Poethko T, Stahl A, Wolf I, Scheidhauer K, Schottelius M, et al. Gluc-Lys([18F]FP)-TOCA PET in patients with SSTR-positive tumors: biodistribution and diagnostic evaluation compared with [111In]DTPA-octreotide. J Nucl Med. 2006;47:566–73.
9. Pauwels E, Cleeren F, Bormans G, Deroose CM. Somatostatin receptor PET ligands - the next generation for clinical practice. Am J Nucl Med Mol Imaging. 2018;8:311–31.
10. Dubash SR, Keat N, Mapelli P, Twyman F, Carroll L, Kozlowski K, et al. Clinical translation of a click-labeled 18F-octreotate radioligand for imaging neuroendocrine tumors. J Nucl Med. 2016;57:1207–13.
11. McBride WJ, Sharkey RM, Karacay H, D'Souza CA, Rossi EA, Laverman P, et al. A novel method of 18F radiolabeling for PET. J Nucl Med. 2009;50:991–8.
12. Laverman P, McBride WJ, Sharkey RM, Eek A, Joosten L, Oyen WJ, et al. A novel facile method of labeling octreotide with 18F-fluorine. J Nucl Med. 2010;51:454–61.
13. Laverman P, D'Souza CA, Eek A, McBride WJ, Sharkey RM, Oyen WJ, et al. Optimized labeling of NOTA-conjugated octreotide with F-18. Tumor Biol. 2012;33:427–34.
14. Long T, Yang N, Zhou M, Chen D, Li Y, Li J, et al. Clinical application of 18F-AlF-NOTA-octreotide PET/CT in combination with 18F-FDG PET/CT for imaging neuroendocrine neoplasms. Clin Nucl Med. 2019;44:452–8.
15. Niedermoser S, Chin J, Wangler C, Kostikov A, Bernard-Gauthier V, Vogler N, et al. In vivo evaluation of 18F-SiFAlin-modified TATE: a potential challenge for 68Ga-DOTATATE, the clinical gold standard for somatostatin receptor imaging with PET. J Nucl Med. 2015;56:1100–5.
16. Wangler C, Waser B, Alke A, Iovkova L, Buchholz HG, Niedermoser S, et al. One-step (18)F-labeling of carbohydrate-conjugated octreotate-derivatives containing a silicon-fluoride-acceptor (SiFA): in vitro and in vivo evaluation as tumor imaging agents for positron emission tomography (PET). Bioconjug Chem. 2010;21:2289–96.
17. Pfeifer A, Knigge U, Binderup T, Mortensen J, Oturai P, Loft A, et al. 64Cu-DOTATATE PET for neuroendocrine tumors: a prospective head-to-head comparison with 111In-DTPA-octreotide in 112 patients. J Nucl Med. 2015;56:847–54.