RESEARCH ARTICLE

Recent Advances in Quantitative Dynamic PET Imaging of Neuroendocrine Tumors

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Abstract

Dynamic positron emission tomography (PET) imaging is a standard art of molecular imaging technology for visualization and quantitative assessment of biochemical and physiopathological activity at cellular and molecular levels in humans and laboratory animals. Tracer kinetic modeling approach developed and validated in last decades is now widely used to extract parameters from dynamic PET data. In the study of neuroendocrine tumors (NETs), the kinetic parameters such as tracer uptake rate constant K_i estimated from dynamic PET with FDA approved ^{18}F-FDG and ^{68}Ga-DOTATATE tracers are suggested to improve the accuracy of NET detection, characterization, grading, staging, and predicting/monitoring NET responses to treatment including peptide receptor radionuclide therapy. The whole-body parametric K_i images generated from shortened dynamic PET using robust parametric imaging algorithm such as machine learning-based approach is potential for clinical and research in NET. In addition, dynamic PET can provide valuable information, such as biological distribution and radiation dose in tissue, in the study of new radioactive tracer in NET. It is expected that quantitative dynamic PET imaging in NET will be widely used for the imaging of somatostatin receptors and evaluation of therapeutic drugs and probes.

1. Introduction

Neuroendocrine tumors (NETs) are often used to refer to the low-proliferating, well-differentiated neuroendocrine neoplasms (NENs), which are a heterogeneous group of malignancies originating from peptidergic neurons and neuroendocrine cells. As an orphan disease comprising with 2% of all malignancies, NETs had a prevalence of more than 6-fold increase from 1973 to 2012 with 171,321 in the United States in 2014.[1] It could correlated with the new definitions and classifications of NETs, the advent of new diagnostic instrumentations, and the increased understanding among physicians.[2] The main characteristics of NETs are that they may occur in any organ of the neuroendocrine system and may be small in size, but with a wide spectrum of clinical symptoms and behaviors.[3] Variations in these characteristics generally make it difficult to diagnose and, therefore, the optimal route of treatment for patients may be different.

Several conventional anatomic imaging methods are available for tumor localization, such as chest radiography or CT for bronchial NETs. However, most NETs that may be small in size or deep in position, such as small bowel tumors, are challenging to detect, especially in the early stage.[4] And it is considered that magnetic resonance imaging (MRI), CT scan, and ultrasonography generally have a lower sensitivity for the identification of gastroenteropancreatie NETs (GEP-NETs).[5] With the continuous development of radiotracers, nuclear medicine imaging has become an important diagnostic and evaluation tool for NETs. By combining with overexpressed molecular biomarkers, primary and metastatic lesions can be accurately detected at the early stage, without further radiation exposure.[6]

A unique feature of NETs is their extremely higher expression of somatostatin receptors (SSTR) in tumors than in the normal tissues. Radionuclide labeled somatostatin analogues provides a broad application prospect in NETs for qualitative, localization, even quantitative diagnosis and peptide receptor radionuclide therapy (PRRT).[7] Positron emission tomography (PET) with ^{68}Ga-DOTA-peptide was considered the first-line diagnostic imaging modality for NETs and a valuable tool for PRRT, because of higher affinity to SSTR in excess of ^{111}In-octreotide, excellent signal-to-noise ratios, and spatial resolution over single photon emission computed tomography (SPECT).[8,9] Conversely, the highly proliferating, poorly differentiated NENs, which known as neuroendocrine carcinomas (NECs), are more suitable for ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET because of high malignant grade, low expression of SSTR, and high glycolytic metabolism.[10]

Dynamic PET imaging, which can better play the characteristics of functional PET imaging, is an advanced imaging technology based on the theory of pharmacokinetics and a powerful analytical tool in the study field of radiolabeled somatostatin analogues.[11] More valuable information about the kinetics of the

radiotracer, including absorption, distribution, metabolism and excretion, can be provided by dynamic PET rather than static PET which only shows standard uptake value (SUV) images at a certain time after injection. Moreover, in the studies of the receptors in vivo, it has been found that the parameters of a novel radiolabeled ligand, such as biological half-life, receptor occupancy, and dosing regimen, can be determined by a limited number of dynamic PET scans.[12] It greatly improves the efficiency and saves the cost in comparison with the traditional methods of drug analysis. This review aims to offer a complete overview of parameters by dynamic PET, SUV and K_i, parametric K_i images, and radiopharmaceuticals biodistribution differences.

2. Kinetic modeling of dynamic PET

Although dynamic PET scanning is more time consuming, its main advantage over the whole-body protocols and visual evaluation by static PET is that it provides more quantitative data that can reflect the dynamic process of radiotracers accumulation in vivo.[13] The most commonly used somatostatin analogs labeled with ^{68}Ga are ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE. These ^{68}Ga-DOTA-peptides which binds primarily to SSTR2,[14] has been demonstrated a group of excellent radiopharmaceuticals for diagnosis and staging of NETs. Application of pharmacokinetic parameters in dynamic PET is scarce, however, have great significance for subsequent therapy to patients in NETs by PRRT.

Koukouraki et al. (2006)[15] analyzed the parameters in dynamic ^{68}Ga-DOTATOC PET, including the rate constants (K_1, k_2, k_3, k_4) and fractional blood volume (V_b) by a two-tissue compartment model with a blood compartment. The study data showed that a high global SUV is not necessarily related to high receptor internalization, which probably because of the cooperative effects by blood volume, receptor binding and internalization. The results demonstrated that the model parameters (K_1, k_2, k_3, k_4 and V_b) had different effects on SUV. If three variables of the five parameters were selected, K_1 (the receptor binding), k_3 (the cellular internalization) and V_b were relatively important, with an effect of K_1 and V_b greater than that of k_3. But in general of these kinetic parameters, K_1 was of the greatest value in affecting the global SUV. The study suggested that the different kinetic factors, which affected the uptake of ^{68}Ga-dotatoc in lesions, could be separated by dynamic PET, and had a more precise evaluation value in NET.

The increased uptake of ^{18}F-FDG, which reflects tumor viability and aggressiveness, has certain significance in prognostic evaluation of NENs.[16] NETs generally demonstrate poor uptake of ^{18}F-FDG because of slow growth and well differentiation, but evidently concentrate of ^{68}Ga-DOTA-peptides. Therefore, ^{68}Ga-DOTA-peptides were often cooperated with ^{18}F-FDG for determination of the biological classification in NENs pre-therapeutically. The kinetics of ^{18}F-FDG and ^{68}Ga-DOTATOC were compared further in

the subsequent research by Koukouraki et al.[17] Both ^{18}F-FDG and ^{68}Ga-DOTATOC showed the global SUV varied greatly in different lesions, which mean the uptake was influent by different biological parameters. The results of multivariate analysis proved that the rate constants (K_1, k_2, k_3, k_4), which showed no significant correlation for the two tracers, were specific characteristics of tracers.

Unlike K_1 as the major parameter to kinetic of ^{68}Ga-DOTATOC, the uptake of ^{18}F-FDG was affected mostly by V_b. The reason argued by the author was that the dependency on the blood volume in the low-uptake areas was higher than that in the high-uptake regions, which made ^{18}F-FDG uptake was influenced mainly by the fractional blood volume (V_b), instead of glucose transporters and the phosphorylation rate. Fractal dimension (FD) is another kinetic parameter to reflect the chaotic distribution of the tracer in primary tumors and metastases. High FD of the two tracers in the results were presumption to the correlation with more aggressive growth (18F-FDG) and more heterogeneous distribution of the SSTR2 (^{68}Ga-DOTATOC).

The affinity bind to subtypes of SSTR are slightly different among the three ^{68}Ga-DOTA-peptides. ^{68}Ga-DOTATATE has the highest affinity for SSTR2 while ^{68}Ga-DOTATOC also binds to SSTR5.[14] ^{68}Ga-DOTANOC targets a broader range of somatostatin subtype receptors, including SSTR2, SSTR3, and SSTR5.[18] The kinetic characteristics of ^{68}Ga-DOTA-peptides were compared by Soto-Montenegro et al.[18] in his study. By applying standard Logan graphical analysis for a two-tissue reversible compartmental model, the volume of distribution (V_t) was computed for assessment from the dynamic study. In his investigation, ^{68}Ga-DOTATOC showed no significant differences in V_T by compared with ^{68}Ga-DOTATATE, but both of the two tracers demonstrated higher V_T in the tumor than ^{68}Ga-DOTANOC, although the latter has affinity for SSTR2, SSTR3 and SSTR5. Consequently, no more advantages in V_T could be emerged for a tracer with affinity bind to more subtypes of SSTR.

3. SUV and K_i

The standardized uptake value (SUV) is the most commonly used parameter to measure radiotracer uptake of lesions, distinguish changed areas or lesions with abnormal metabolism, and indirectly reflect radiotracer consumption rate.[19] Although it is convenient for detection, diagnosis and observation of therapeutic response, it is often limited as a semi-quantitative parameter by extravasations, recording of the injected activity, the variation of the absorption by target and non-target organs, and differences between plasma and body volume.[20]

The compartment model is considered the gold standard in PET quantification.[21] The neuroreceptor binding model is one of the well-established compartmental models in PET for analyzing receptor-ligand system. K_i is a kinetic parameter calculated by fitting the

compartment model, that represents the radiopharmaceutical uptake rate and incorporates both internal net transport and tracer trapping in the tissue ($K_i = K_1k_3/(k_2+k_3)$).[22] Due to its simplicity in calculation, macro-parameter K_i is widely estimated by a graphical analysis, Patlak plot, for quantification of radioligand-receptor dynamic PET with slow kinetics.[23] The calculation of K_i by adding the input function was thought to be capable of correcting the main limitations of SUV.[20]

Assumed K_i of ^{68}Ga-DOTA-peptide as the gold standard, a few of studies have attempted to explore some parameters derived from static images, in order to determine which one might better reflect the SSTR expression levels in NETs. In their study on dynamic and static ^{68}Ga-DOTATOC PET during PRRT, Van et al.[24] compared a series of static parameters with K_i, including the SUV_{max} and SUV_{mean} of the tumors, and the SUV_{ratios} values normalized by the background organs. The results conclusively show that $SUV_{max/mean}$ values of the tumoral lesions on the static ^{68}Ga-DOTATOC PET correlate better with K_i than the normalized values, so the $SUV_{max/mean}$ values of the static images should be the parameter of choice in therapy assessment.

As a reasonable metabolic index to evaluate the malignant degree or therapeutic response of tumors, SUV can be used in FDG PET because of the principle of FDG uptake by all tissues in the body. But in the NETs, the measurement results of SUV may be affected due to the distribution volume of somatostatin receptors limited in some tissues. The changes after treatment of tumor SUV in ^{68}Ga-DOTATOC PET/CT showed uncorrelated to the therapeutic results of PRRT by a study,[25] which suggested that SUV may not be applicable to the therapy evaluation of NETs. Tracer kinetic parameters by dynamic PET, rather than SUV, might reflect the receptor density more accurately by contributing the additional dimensions of time and accumulation rate.[26] The steady-state K_i, which was determined by nonlinear regression of an irreversible 2-tissue-compartment model and the Patlak method, is considered a better index of reflecting the receptor concentration.

In the study by Velikyan et al.,[26] analyzed by Patlak and the compartment model respectively, K_i of the two tracers (^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE) had a good correlation. But Linear correlation was not found between SUV and K_i in the study. SUVs no longer increased and achieved saturation for K_i values greater than 0.2 $mL/cm^3/min$. It was considered by author that high value in SUV (SUV>20-25) may not accurately reflect SSTR density, while K_i might be an available result indicator for SSTR density quantification. Faster blood clearance in patients with higher receptor expression was thought to be the reason for the above result in the subsequent study by Ilan et al.[27] It is likely that almost all peptides in the plasma were cleared at the early detection stage because of the large amount of SSTR in some patients, resulting in obvious saturation of the tumor SUV values. Conversely, a linear relation

between K_i and the tumor-to-blood ratio (TBR) was found in this article. Therefore, TBR was supposed to be a better parameter for reflecting SSTR density than SUV. For measurement and treatment monitoring of NETs, TBR would be a valuable tool for semi-quantitative evaluation of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE tumor uptake. Therefore, K_i not only contributed to the analysis of receptor density and pharmacokinetics, but also had great value for the search for relevant static parameters. The SUV could be used to approximate K_i in FDG PET with a number of physiological assumptions.[28]

4. Parametric K_i images

It is easy to achieve with low computation cost for the region of interest (ROI) based kinetic modeling. In contrast, another approach for deriving tracer kinetics from dynamic PET data is parameter imaging, which is more sensitive to noise and requires more demanding calculation.[29] Parametric images characterized by kinetic parameters for every image voxel, is considered more suitable for studying heterogeneous tracer uptake in tissue because of providing four-dimensional distribution.[30]

Quantitative and accurate parametric K_i images can display precisely calculated K_i in voxel level reliably, which has better contrast and clinical application value than whole-body scanning. In the study of Ilan, et al.,[31] a method to obtain parametric K_i images was introduced: first, a basis function method (BFM) was implemented on the irreversible 2-tissue-compartment model, and then the in-house-developed software was used in MATLAB to perform Patlak method analysis on PET data 15-45 minutes after drug administration. Robust parametric imaging algorithms including spatially constrained approach, direct parametric image reconstruction, and machine learning-based method have been proposed to generate Ki images from shortened dynamic FDG and ^{68}Ga-DOTATATET PET.[32-35]

High correlation and agreement with no significant bias were found in the study between the VOI based K_i (K_i-NLR) values and the parametric based K_i (K_i-BFM and K_i-Patlak) values for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE. This suggests that parametric K_i images computed by BFM and Patlak were suitable for both radiotracers. On the other hand, values of low K_i presented greatly overestimated by parametric images compared with K_i-NLR, and high K_i presented mildly underestimated. This is actually due to the fact that the K_i-NLR analysis based on VOI may have underestimated the K_i value of the tumor. The parametric based K_i values, which are much lower in the surrounding tissue and will not spill over to affect the tumor uptake, represented the actual tumor K_i to a greater extent and thus be higher than the NLR value. Physiological liver background uptake often influenced the accuracy of uptake measurement of liver metastatic tumor. Compared with the whole body SUV image based on VOI, parametric image can provide better image contrast for both tracers, which is

more obvious in ^{68}Ga-DOTATATE. This is consistent with Ki estimates in 60-min dynamic FDG PET study between NLR and Patlak plot method.[36]

5. Radiopharmaceuticals biodistribution differences

A case of pancreatic NET with liver metastasis detected by dynamic ^{18}F-FDG and ^{68}Ga-DOTATOC PET was reported by Sänger et al..[37] Both of the two tracers image sets showed very early signal increase in a hyper vascular metastatic lesion of liver over the first 28s. However, decreased uptake ^{18}F-FDG was found by the time-activity curve and visual inspection at 60-90s, while continuously increase uptake of ^{68}Ga-DOTATOC by the metastasis tumor. Although recent publications have suggested that ^{18}F-FDG dynamic PET has the potential to characterize liver lesions hyper vascularization, it seemed from this study that the concept of which may vary in the use of tracers with faster kinetics, such as ^{68}Ga-DOTATOC.

Previous studies suggest that early dynamic PET can be used as a potential alternative to contrast-enhanced CT for the imaging of arterial hypervascularization in liver tumors. Sänger et al.[38] discussed in detail whether liver metastases of NET can be reliably detected by ^{68}Ga-DOTATOC in the condition of somatostatin receptors (positive or negative) and (with or without) hypervascularity. Although radio activities of all lesions increased in the early arterial phase (16-40s), the data in the subsequent stage performed varies among the four subgroups (hypervascularized/receptor positive (HV^+R^+), HV^-R^+, HV^+R^-, HV^-R^-). The signal growth of HV^+ subgroups were significantly higher than that of HV^- groups regardless of the receptors (positive or negative). The signal in HV^+R^- subgroup showed a rapid peak, while a steady increase of signal in HV^+R^+ subgroup was found, which different from ^{18}F-FDG dynamic PET results. Therefore, when the receptor density is low (e. g. HV^+R^- and HV^-R^-), early arterial blood flow (via increased influx) is the main factor affecting the signal, by which more radioactive tracers are accumulated in the HV^+R^- subgroup; the different manifestations of the data, when the receptor was the main influencing factor (e.g. HV^-R^+ and HV^-R^-), can be explained by the rapidity of tracer kinetics and specific receptor binding. ^{68}Ga-DOTATOC dynamic PET was suggested by authors a useful tool for characterizing hepatic NET metastases, which can be used as an alternative or adjunct to contrast-enhanced CT.

Dynamic PET can also provide valuable information of new radiopharmaceuticals on the biodistribution and dosimetry in normal tissues. For example, the latest biological distribution studies in mice have showed that ^{68}Ga-DOTA-JR11 and ^{68}Ga-NODAGA-JR11 (^{68}Ga-OPS202), a type of SSTR antagonists, had higher tumor uptake than ^{68}Ga-DOTATATE in PET, which provided experimental evidence for further clinical evaluation.[39]

In the first-in-human investigation by Krebs et al, the bio-distribution of

^{68}Ga-DOTA-JR11 was impressive with little tracer uptake in normal parenchymal organs, especially in liver.[40] A higher quality image and more sensitive detection of liver metastases resulted by rapidly uptake of ^{68}Ga-DOTA-JR11 in tumor tissue and the low background activity in liver.[41] Nicolas et al. compared the ability of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC in detecting liver lesions and malignant lesions.[42] The results showed that ^{68}Ga-OPS202 could detect significantly more lesions than the latter, and the tumor-to-background ratios also showed higher uptake in liver lesions, which mainly related to the significant reduced uptake by the liver background of ^{68}Ga-OPS202. Compared with ^{68}Ga-DOTATOC, therefore, the lower uptake of ^{68}Ga-OPS202 in liver, instead of the higher uptake by liver lesions, result in the higher tumor-to-background ratio, which made the liver lesions easier to be detected.

6. Conclusions and prospects

As a quantitative approach of tracer uptake based on compartment modeling, dynamic PET can effectively improve the feature recognition and therapeutic response monitoring of tumors. It can help people understand the dynamic interaction between receptor density and radioactive ligand by monitoring the image information of the spatial distribution of radioactive ligand and its change over time in vivo. But some noisy information, such as inherent statistical noise associated with radioactive decay and physiological factors, may interfere with image analysis.[43] Several quantitative parameters, which characterize the distribution of receptors in vivo and/or the binding process of receptor to ligand, can be refined from these dynamic information by tracer dynamic modeling.[44] Therefore, the application of dynamic PET in neuroendocrine tumors has gained increasing attentions in the related receptor distribution patterns and the development of novel drugs.

However, long image acquisition and single bed-position heavily restrict the application of dynamic PET in clinical practice,[45] since the main advantages of PET lie in its fast scan in limited time and whole-body assessment of diffuse diseases. Recent developments on whole-body parametric imaging can meet the requirements of large axial fields of view and continuous bed motion in both PET hardware and algorithms.[46] This repeatable, highly reliable, quantitative technique that does not add additional workload is of great value in differentiating malignancies from infection/inflammation, improving tumor staging assessment and accurate estimation of early treatment response.[47] In consideration of its long scan duration may influence patient throughput and comfort, whole-body dynamic PET may be used as a powerful supplement of static PET as so far, rather than replace it.

7. Reference

1 Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. *CA Cancer J Clin*. 2018;68(6):471-487.

2 Maffione AM, Karunanithi S, Kumar R, Rubello D, Alavi A. Nuclear medicine procedures in the diagnosis of NET: a historical perspective. *PET Clin*. 2014;9(1):1-9.

3 Ambrosini V, Morigi JJ, Nanni C, Castellucci P, Fanti S. Current status of PET imaging of neuroendocrine tumours ([18F]FDOPA, [68Ga]tracers, [11C]/[18F]-HTP). *Q J Nucl Med Mol Imaging*. 2015;59(1): 58-69.

4 Ethun CG, Postlewait LM, Baptiste GG, McInnis MR, Cardona K, Russell MC, et al. Small bowel neuroendocrine tumors: a critical analysis of diagnostic work-up and operative approach. *J Surg Oncol*. 2016;114(6):671-676.

5 Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia*. 2017;19(12):991-1002.

6 Barollo S, Bertazza L, Watutantrige-Fernando S, Censi S, Cavedon E, Galuppini F, et al. Overexpression of L-type amino acid transporter 1(LAT1) and 2(LAT2): novel markers of neuroendocrine tumors. *PloS One*. 2016;11(5):e0156044.

7 Mojtahedi A, Thamake S, Tworowskal, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging*. 2014;4(5):426-434.

8 Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. *Radiographics*. 2015;35(2): 500-516.

9 Maffione AM, Karunanithi S, Kumar R, Rubello D, Alavi A. Nuclear medicine procedures in the diagnosis of NET: a historical perspective. *PET Clin*. 2014;9(1):1-9.

10 Carideo L, Prosperi D, Panzuto F, Magi L, Pratesi MS, Rinzivillo M, et al. Role of combined [68Ga]Ga-DOTA-SST analogues and [^{18}F]FDG PET/CT in the management of GEP-NENs: a systematic review. *J Clin Med*. 2019;8(7). pii: E1032.

11 Muzi M, O'Sullivan F, Mankoff DA, Doot RK, Pierce LA, Kurland BF, et al. Quantitative assessment of dynamic PET imaging data in cancer imaging. *Magn Reson Imaging*. 2012;30(9):1203-1215.

12 Lammertsma AA. Forward to the past: the case for quantitative PET imaging. *J Nucl Med*. 2017;58(7):1019-1024.

13 Dimitrakopoulou-Strauss A, Pan L, Strauss LG. Quantitative approaches of dynamic FDG-PET and PET/CT studies (dPET/CT) for the evaluation of oncological patients. *Cancer Imaging*. 2012;12:283-289. doi:

10.1102/1470-7330.2012.0033

14 Alexander N, Vali R, Ahmadzadehfar H, Shammas A, Baruchel S. Review: The role of radiolabeled DOTA-conjugated peptides for imaging and treatment of childhood neuroblastoma. *Curr Radiopharm*. 2018;11(1):14-21. doi: 10.2174/1874471011666171215093112.

15 Koukouraki S, Strauss LG, Georgoulias V, Schuhmacher J, Haberkorn U, Karkavitsas N, et al. Evaluation of the pharmacokinetics of 68Ga-DOTATOC in patients with metastatic neuroendocrine tumours scheduled for 90Y-DOTATOC threrapy. *Eur J Nucl Med Mol Imaging*. 2006;33(4):460-466.

16 Zhang P, Yu J, Li J, Shen L, Li N, Zhu H, et al. Clinical and prognostic value of PET/CT imaging with combination of 68Ga-DOTATATE and 18F-FDG in gastroenteropancreatic neuroendocrine neoplasms. *Contrast Media Mol Imaging*. 2018;2018:2340389. doi: 10.1155/2018/2340389. eCollection 2018.

17 Koukouraki S, Strauss LG, Georgoulias V, Eisenhut M, Haberkorn U, Dimitrakopoulou-Strauss A. Comparison of the pharmacokinetics of 68Ga-DOTATOC and [18F]FDG in patients with metastatic neuroendocrine tumours scheduled for 90Y-DOTATOC threrapy. *Eur J Nucl Med Mol Imaging*. 2006;33(10):1115-1122.

18 Soto-Montenegro ML, Peña-Zalbidea S, Mateos-Pérez JM, Oteo M, Romero E, Morcillo MÁ, et al. Meningiomas: a comparative study of 68Ga-DOTATOC, 68Ga-DOTANOC and 68Ga-DOTATATE for molecular imaging in mice. *PloS One*. 2014;9(11):e111624. doi: 10.1371/journal.pone.01116224. eCollection 2014.

19 Park SY, Kim HS, Song HJ, Dong KR, Chung WK, Yeo HY. A study on usefulness evaluation of SUV measured in mini-PACS for each one of PET/CT equipment. *J Digit Imaging*. 2015;28(1):62-67. doi: 10.1007/s10 278-014-9724-x.

20 Prando S, Carneiro CG, Robilotta CC, Sapienza MT. Comparison of different quantification methods for 18F-fluorodeoxyglucose-positron emission tomography studies in rat brains. *Clinics (Sao Paulo)*. 2019;74:e1273. doi: 10.6061/clinics/2019/e1273. eCollection 2019.

21 Ottoy J, Verhaeghe J, Niemantsverdriet E, Wyffels L, Somers C, De Roeck E, et al. Validation of the semiquantitative static SUVR method for ^{18}F-AV45 PET by pharmacokinetic modeling with an arterial input function. *J Nucl Med*. 2017;58(9):1483-1489. doi: 10.2967/jnumed.116.184481. Epub 2017 Mar 23.

22 Karakatsanis NA, Lodge MA, Tahari AK, Zhou Y, Wahl RL, Rahmim A. Dynamic whole-body PET parametric imaging: I. concept, acquisition protocal optimization and clinical application. *Phys Med Biol*. 2013;58 (20):7391-7418. doi: 10.1088/0031-9155/58/20/7391. Epub

2013 Sep 30.

23 Zhou Y, Ye W, Brasić JR, Wong DF. Multi-graphical analysis of dynamic PET. *Neuroimage*. 2010 Feb 15;49(4):2947-2957. doi: 10.1016/j.neuroimage.2009.11.028. Epub 2009 Nov 17. PMID: 19931403; PMCID: PMC2824569.

24 Van Binnebeek S, Koole M, Terwinghe C, Baete K, Vanbilloen B, Haustermans K, et al. Dynamic 68Ga-DOTATOC PET/CT and static image in NET patients. Correlation of parameters during PRRT. *Nuklearmedizin*. 2016;55(3):104-114. doi: 10.3413/Nukmed-0742-15-05. Epub 2016 Apr 8.

25 Gabriel M, Oberaurer A, Dobrozemsky G, Decristoforo C, Putzer D, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. *J Nucl Med*. 2009;50(9):1427-1434. doi: 10.2967/jnumed.108.053421. Epub 2009 Aug 18.

26 Velikyan I, Sundin A, Sörensen J, Lubberink M, Sandström M, Garske-Román U, et al. Quantitative and qualitative intrapatient comparison of 68Ga-DOTATOC and 68Ga-DOTATATE: net uptake rate of accurate quantfication. *J Nucl Med*. 2014;55(2):204-210. doi: 10.2967/jnumed.113.126177. Epub 2013 Dec 30.

27 Ilan E, Velikyan I, Sandström M, Sundin A, Lubberink M. Tumor-to-Blood Ratio for Assessment of Somatostatin Receptor Density in Neuroendocrine Tumors Using 68Ga-DOTATOC and 68Ga-DOTATATE. *J Nucl Med*. 2020;61(2):217-221. doi:10.2967/jnumed.119.228072

28 Huang SC. Anatomy of SUV. Standardized uptake value, *Nucl Med and Biol* 2000; 27(7), 643-646.

29 Seo S, Kim SJ, Lee DS, Lee JS. Recent advances in parametric neuroreceptor mapping with dynamic PET: basic concepts and graphical analyses. *Neurosci Bull*. 2014;30(5):733-754. doi: 10.1007/s12264-014-1465-9. Epub 2014 Sep 28.

30 Zuo Y, Qi J, Wang G. Relative Patlak plot for dynamic PET parameter imaging without the need for early-time input function. *Phys Med Biol*. 2018;63(16):165004. doi: 10.1088/1361-6560/ aad444.

31 Ilan E, Sandström M, Velikyan I, Sundin A, Eriksson B, Lubberink M. Parametric net influx rate images of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE: quantitative accuracy and improved image contrast. *J Nucl Med*. 2017;58(5):744-749. doi: 10.2967/jnumed.116.180380. Epub 2016 Oct 27.

32. Zhang X, Xie Z, Berg E, Judenhofer MS, Liu W, Xu T, et al. Total-Body Dynamic Reconstruction and Parametric Imaging on the uEXPLORER. *J Nucl Med*. 2020 Feb;61(2):285-291. doi: 10.2967/jnumed.119.230565. Epub 2019

Jul 13. PMID: 31302637.

33. Karakatsanis NA, Casey ME, Lodge MA, Rahmim A, Zaidi H. Whole-body direct 4D parametric PET imaging employing nested generalized Patlak expectation-maximization reconstruction. *Phys Med Biol*. 2016 Aug 7;61(15):5456-5485. doi: 10.1088/0031-9155/61/15/5456. Epub 2016 Jul 6. PMID: 27383991; PMCID: PMC5884686.
34. Karakatsanis NA, Zhou Y, Lodge MA, Casey ME, Wahl RL, Zaidi H, et al. Generalized whole-body Patlak parametric imaging for enhanced quantification in clinical PET. *Phys Med Biol*. 2015 Nov 21;60(22):8643-8673. doi: 10.1088/0031-9155/60/22/8643. Epub 2015 Oct 28. PMID: 26509251; PMCID: PMC4710061.
35. Zhou Y, Yu J, Liu M, Li H, Yang Z, Wahl R. A machine learning-based parametric imaging algorithm for noninvasive quantification of dynamic [68Ga] DOTATATE PET-CT. Journal of Nuclear Medicine. 2019;60:1186-.
36 Y. Zhou, S. C. Huang, and M. Bergsneider, Linear ridge regression with spatial constraint for generation of parametric images in dynamic positron emission tomography studies. *IEEE Transactions on Nuclear Science*, vol. 48, pp. 125-130, 2001.
37 Sänger P, Schierz JH, Marlowe RJ, Freesmeyer M. Detectability of hypervascularity in early dynamic PET depends on tracer kinetics: 18F-FDG versus 68Ga-DOTATOC in hepatic NET matastasis. *Liver Int*. 2014;34(1):161. doi: 10.1111/liv.12192. Epub 2013 May 12.
38 Sänger PW, Freesmeyer M. Early dynamic 68Ga-DOTA-D-Phe1-Tyr3-Octreotide PET/CT in patients with hepatic metastases of neuroendocrine tumors. *Clin Nucl Med*. 2016;41(6):447-453. doi: 10.1097/RLU.0000000000001154.
39 Fani M, Nicolas GP, Wild D. Somatostatin receptor antagonists for imaging and therapy. *J Nucl Med*. 2017;58(Suppl 2):61S-66S. doi: 10.2967/jnumed.116.186783.
40 Krebs S, Pandit-Taskar N, Reidy D, Beattie BJ, Lyashchenko SK, Lewis JS, et al. Biodistribution and radiation dose estimates for ^{68}Ga-DOTA-JR11 in patients with metastatic neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2019;46(3):677-685.
41 Zhu W, Cheng Y, Wang X, Yao S, Bai C, Zhao H, et al. Head-to-head comparison of 68Ga-DOTA-JR11 and 68Ga-DOTATATE PET/CT in patients with metastatic, well-differentiated neuroendocrine tumors: a prospective study. *J Nucl Med*. 2019 Nov 1. pii: jnumed.119.235093. doi: 10.2967/jnumed.119. 235093. [Epub ahead of print]
42 Nicolas GP, Schreiter N, Kaul F, Uiters J, Bouterfa H, Kaufmann J, et al. Sensitivity comparison of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine

tumors: a prospective phase II imaging study. *J Nucl Med*. 2018;59(6):915-921.

43 Maneuski D, Giacomelli F, Lemaire C, Pimlott S, Plenevaux A, Owens J, et al. On the use of positron counting for radio-Assay in nuclear pharmaceutical production. *Appl Radiat Isot.* 2017;125:9-14. doi: 10.1016/j.apradiso. 2017.03.021. Epub 2017 Mar 24.

44 Hardiansyah D, Attarwala AA, Kletting P, Mottaghy FM, Glatting G. Prediction of time-integrated activity coefficients in PRRT using simulated dynamic PET and a pharmacokinetic model. *Phys Med.* 2017; 42:298-304. doi: 10.1016/j.ejmp.2017.06.024. Epub 2017 Jul 22.

45 Rahmim A, Lodge MA, Karakatsanis NA, Panin VY, Zhou Y, McMillan A, et al. Dynamic whole-body PET imaging: principles, potentials and applications. *Eur J Nucl Med Mol Imaging*. 2019;46(2):501-518. doi: 10.1007/s002 59-018-4153-6. Epub 2018 Sep 29.

46 Zhuang M, Karakatsanis NA, Dierckx RAJO, Zaidi H. Quantitative analysis of heterogeneous [^{18}F]FDG static (SUV) vs. Patlak (Ki) whole-body PET imaging using different segmentation methods: a simulation study. *Mol Imaging Biol*. 2019;21(2):317-327. Doi: 10.1007/s11307-018- 1241-8.

47 Leahy R, Boellaard R, Zaidi H. Whole-body parametric PET imaging will replece conventional image-derived PET metrics in clinical oncology. *Med Phys.* 2018;45(12):5355-5358. doi: 10.1002/mp.13266. Epub 2018 Nov 26.

