ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Update on the Role of [^{18}F]FDOPA PET/CT

Gilles N. Stormezand, MD, PhD,* Eline de Meyer,*,† Klaas Pieter Koopmans,* Adrienne H. Brouwers,* G. Luurtsema,* and Rudi A.J.O. Dierckx*

[^{18}F]-dihydroxyphenylalanine ([^{18}F]FDOPA) is a radiopharmaceutical used in a broad spectrum of diseases, including neuroendocrine tumors (NETs), congenital hyperinsulinism, parkinsonian syndromes and neuro-oncology. Genetic analysis and disease specific biomarkers may guide the optimum selection of patients that may benefit most from [^{18}F]FDOPA PET in different stages of several neuroendocrine neoplasms and in congenital hyperinsulinism. For clinical routine in neuro-oncology, indications for [^{18}F]FDOPA PET include tumor delineation and distinguishing between treatment related changes and recurrent disease. New developments as the advent of large axial field of view PET/CT or integrated PET/MRI systems may provide more unique opportunities, such as those related to detection of smaller lesions in primary staging of NETs, dose reduction in children with congenital hyperinsulinism, or possibilities to obtain more extensive noninvasive quantification of cerebral uptake by using image derived input functions. Although the widespread use of [^{18}F]FDOPA has been hampered by complex synthesis methods and high production costs in the past, significant efforts have been undertaken to provide robust GMP compliant synthesis methods with high activity yield and molar activity.

Introduction

[^{18}F]-dihydroxyphenylalanine ([^{18}F]FDOPA) is a radiopharmaceutical used for several indications in oncology and neurodegenerative diseases. [^{18}F]FDOPA was first used in vivo in humans more than four decades ago as described in a hallmark *Nature* paper by Garnett et al., which demonstrated its ability to visualize the dopaminergic system in the basal ganglia.[1] Since then, indications have broadened and its use has been widely explored in different domains, leading to the inclusion of [^{18}F]FDOPA PET scans in international guidelines regarding neurodegenerative disorders, neuro-oncology, congenital hyperinsulinism (CHI) and neuro-endocrine tumors (NETs), including pheochromocytoma (PCC)/paraganglioma (PGG), and medullary thyroid cancer.[2–5] The favorable half-life of 110 minutes of the fluorine-18 radionuclide, alongside the development of automated GMP compliant production methods with higher molar activity, increased activity yield and less complex synthesis modules, could allow for a more widespread use of the tracer.[6] Herein we will focus on the current and future use of [^{18}F]FDOPA, its diagnostic accuracy and ability to be used as a means for measuring treatment response, disease progression and its aid in management in a broad spectrum of diseases.

*Department of Nuclear Medicine and Molecular Imaging, Medical Imaging Center, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
†Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
Address reprint requests to Gilles N. Stormezand, Department of Nuclear Medicine and Molecular Imaging, Medical Imaging Center, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands. E-mail: g.n.stormezand01@umcg.nl

Neuro-Endocrine Tumors

Neuro-endocrine tumors are a heterogenous group of neoplasms which can occur within many different organs. Uptake of [^{18}F]FDOPA in neuro-endocrine tumors is facilitated by the large amino acid transporter (LAT1/4F2gc). [^{18}F]FDOPA follows the same pathway as L-DOPA, a precursor in the catecholamine synthesis pathway. After entering the cell, L-DOPA is converted to L-dopamine by the enzyme aromatic L-amino-acid decarboxylase (AADC) and then stored in synaptic vesicles. Disease specific uptake of [^{18}F]FDOPA may be increased in some instances by premedication with carbidopa, a peripheral decarboxylation blocking

https://doi.org/10.1053/j.semnuclmed.2024.09.004

agent. NET's can be subdivided in grades 1-3 and neuroendocrine carcinoma as a separate category, based on the number of mitoses and the proliferation marker Ki-67 index.[7] Neuro-endocrine tumors usually show high somatostatin receptor expression (mainly somatostatin receptor subtype 2), which can be visualized using ^{68}Gallium labeled somatostatin labeled analogs ([^{68}Ga]SSA). In comparison to [^{68}Ga]SSA PET, [^{18}F]FDOPA has an inherent advantage of superior spatial resolution, owing to less kinetic energy after emission of the positron from fluorine-18 than gallium-68, leading to a smaller positron range.[8] Fluorine-18 labelled SSA PET alternatives have been investigated with promising results, but have not yet been widely adopted.[9] [^{68}Ga]SSA PET has the advantage that it can be used to select those patients that would benefit from peptide receptor radionuclide therapy (PRRT).

The sensitivity of [^{18}F]FDOPA for the detection of NET activity depends on its origin, with highest diagnostic accuracy for NETs of the midgut and somewhat less for the foregut.[10] Experiences for primary lung NET's are less favorable.[11] Although uptake via the LAT is specific for neuroendocrine tumors, false positive uptake has been described to occur rarely, mostly due to other malignancy[12] False negative findings are more prevalent in NETs originating from the thymus, duodenum and in insulinoma. In the *Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-conjugated somatostatin receptor targeting peptides and [^{18}F]FDOPA* it is described that [^{18}F]FDOPA is approved in several European countries for diagnosis (glomus tumor, pheocromocytoma (PCC), paraganglioma (PGG), congenital hyperinsulinism), staging (PCC, PGG, and well differentiated neuroendocrine tumors of the digestive tract) and in case of reasonable suspicion of recurrence of residual disease (PCC, PGG, medullary cancer, well differentiated NET's of the digestive tract, endocrine digestive tumors with negative somatostatin receptor scintigraphy).[3] These indications will be discussed briefly in this section.

Pheochromocytoma and Paraganglioma

PCC's and PGG's are neuro-endocrine tumors arising from the neural crest and can be found in the adrenal medulla (PCC) or in sympathetic and parasympathethic ganglia or the autonomous nervous system (PGG).[13] Indications for scanning procedure involve elevated plasma or urinary metanephrines or clinical symptoms related to catecholamine excess but can also be performed when adrenal lesions increase in size in genetically predisposed subjects.[14] Few studies have compared [^{18}F]FDOPA to [^{68}Ga]SSA PET in diagnosing PCC. Results indicate that [^{18}F]FDOPA may be more sensitive for detecting primary PCC (sporadic or related to non-SDHx mutations),[15] whereas [^{68}Ga]SSA PET performs equally well or slightly superior for detecting extra-adrenal disease and SDHx-mutation related disease. An example of the added value of [^{18}F]FDOPA PET over [^{68}Ga]SSA in the detection of PCC is shown in Figure 1. Recently proposed scanning algorithms for nuclear imaging in PCC and PGG also includes [^{18}F]FDG PET as a third choice, when [^{18}F]FDOPA or [^{68}Ga]SSA are not available, or as a second choice in case of extra-adrenal, multifocal or metastatic disease.[16]

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) accounts for approximately 2 percent of thyroid carcinoma's, yet is related to a significant percentage of thyroid cancer related deaths (approximately 15 percent) and a relatively high proportion of patients has metastases upon primary presentation.[17] It is a neuroendocrine tumor originating from parafollicular C cells of the thyroid gland. The clinical presentation varies between the sporadic (75%) and the hereditary form (25%), related to multiple endocrine neoplasia (MEN). Surgery is the only curative treatment, consisting of total thyroidectomy and neck dissection.[18] High accumulation of [^{18}F]DOPA in MTC exists as both LAT expression and AADC activity are upregulated.[19] Although ultrasound is considered to be the primary imaging modality of choice for diagnosis and detection of lymph nodes metastases in MTC, a recent study has shown high sensitivity of [^{18}F]FDOPA PET for detection of the primary lesion in this setting, as well as for lymph node metastases in the lateral compartment of the neck, but less so in the central compartment, possibly due to small size. In this series, [^{18}F]FDOPA PET showed the additional advantage of detecting distant metastasis in a small portion of patients, which may alter patient management.[20] However, additional evidence may be mandatory to recommend [^{18}F]FDOPA PET for staging before treatment and for evaluating treatment response.[21] In the postoperative period, secretae from parafollicular C-cells such as serum calcitonin (Ctn), procalcitonin (PCT) and carcinoembryonic antigen (CEA) can be used as tumor markers and guide selection of those patients who benefit most from [^{18}F]FDOPA PET scanning, with the American Thyroid Association (ATA) advising additional imaging when postoperative Ctn values higher than 150 pg/ml.[22] A shortened CT/CEA doubling time (within 24 months) could also prompt additional investigation. The detection rate of [^{18}F]FDOPA on a per patient base has been estimated to be around 72%.[23] A negative [^{18}F]FDOPA PET scan has been associated with a longer progression-free and disease specific survival.[24] When compared with [^{18}F]FDG, [^{18}F]FDOPA has higher efficacy for detection of metastases in lymph nodes, liver and the bone, whereas [^{18}F]FDG PET may be more sensitive for lung metastases and can be used as a back-up when [^{18}F]FDOPA PET and [^{68}Ga]SSA PET are not available.[25] It should also be considered in aggressive subtypes, e.g. in subjects with shorter Ctn/CEA doubling times, as the [^{18}F]FDG uptake correlates with poor differentiation of malignant MTC cells. In these instances, highly [^{18}F]FDG avid disease may show no [^{18}F]FDOPA uptake[26] Figure 2 shows an example of combined [^{18}F]FDOPA and [^{18}F]FDG PET imaging in one patient in the setting of recurrent disease. If [^{18}F]FDOPA is unavailable, [^{68}Ga]SSA PET could be the functional imaging modality of

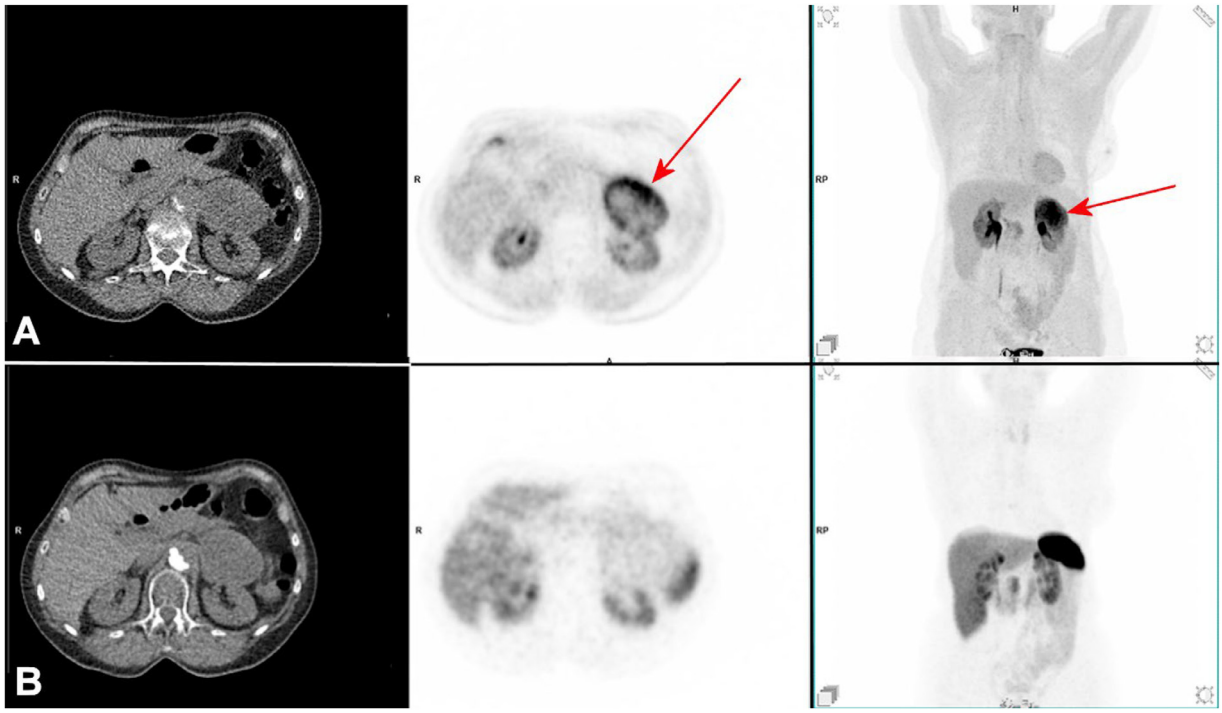

Figure 1 A 66 year old patient presented with a left adrenal mass, which was detected as an incidental finding in the work-up of anemia. Laboratory findings showed increased plasma metanephrines, raising the suspicion of PCC. Initially, a [68Ga]DOTATOC PET scan was performed with no specific uptake at the location of the adrenal mass (B). A few weeks later a [18F]FDOPA PET scan revealed markedly increased uptake in the adrenal mass (red arrows), highly suggestive of PCC (A). No other sites of disease were detected. After surgical resection, the diagnosis of PCC was confirmed, with a low Ki proliferation index (<1%) and no associated genetic mutations (sporadic form).

choice, although its detection rate for recurrent MTC has been estimated to be somewhat lower (around 64%).[25]

Gastrointestinal NETs

Around 55 percent of NETs develop in the gastrointestinal tract, making it the most prevalent primary site.[27] Within the GI tract, the small bowel is the most common site of NETs, followed by the rectum and the appendix.[28] Gastrointenstinal NETs are slow-growing tumors with distinct histological features. The clinical presentation may depend on the primary site and whether or not these tumors are releasing endocrine substances (secretory NETs). In non-secretory NETs symptoms may arise late due to mass effect. Alternatively, these may be detected as an incidental finding after surgery or endoscopy. For disease monitoring, serum chromogranin A is the most often used biomarker.[29] In the midgut, a sensitivity and specificity of 93% and 89% have been described.[10] Accurate staging is of importance in many patients as it may guide further treatment plans including surgery with curative intent, which may still be possible if the metastatic spread is limited. A meta-analysis comparing [18F]FDOPA with [68Ga]SSA PET in intestinal NETs demonstrated comparable sensitivity on a per patient basis, but a significantly higher sensitivity of [18F]FDOPA on a lesion basis, particularly with respect to detection of lesions in the liver and bone and when high levels of serotonin or 5-HIIA were present.[30,31]

Congenital Hyperinsulinism

[18F]FDOPA PET also plays a role in management of congenital hyperinsulinism (CHI), a rare disease that develops in approximately 1 to 30000 to 50000 live births.[32] Initial treatment may start with Diaxozide, which attempts to inhibit insuline release by opening the KATP channel of pancreatic beta-cells. Other treatment modalities are octreotide, or glucagon when urgent treatment of hypoglycemia is needed. Congenital hyperinsulinism can be the result of either focal or diffuse pancreatic disease, and can be distinguished easily via [18F]FDOPA PET. Focal lesions may be hard to identify using conventional imaging techniques using CT and MRI. Yet, its detection may be crucial as up to 97 percent of patients are cured with surgery and it can influence whether to perform a lesionectomy or a near total pancreatecomy.[33] Histopathologically, focal lesions correspond to beta-cell adenomatosis, whereas in the diffuse form there is enlargement of islet cell nuclei without an overall increase in the volume of endocrine tissue.[34] Genetic analysis guides the selection of patients suited for [18F]FDOPA imaging as it can predict the presence of a focal lesion and can prevent unnecessary imaging in subjects with diffuse disease.[35] The discontinuation of medication for congenital hyperinsulinism prior

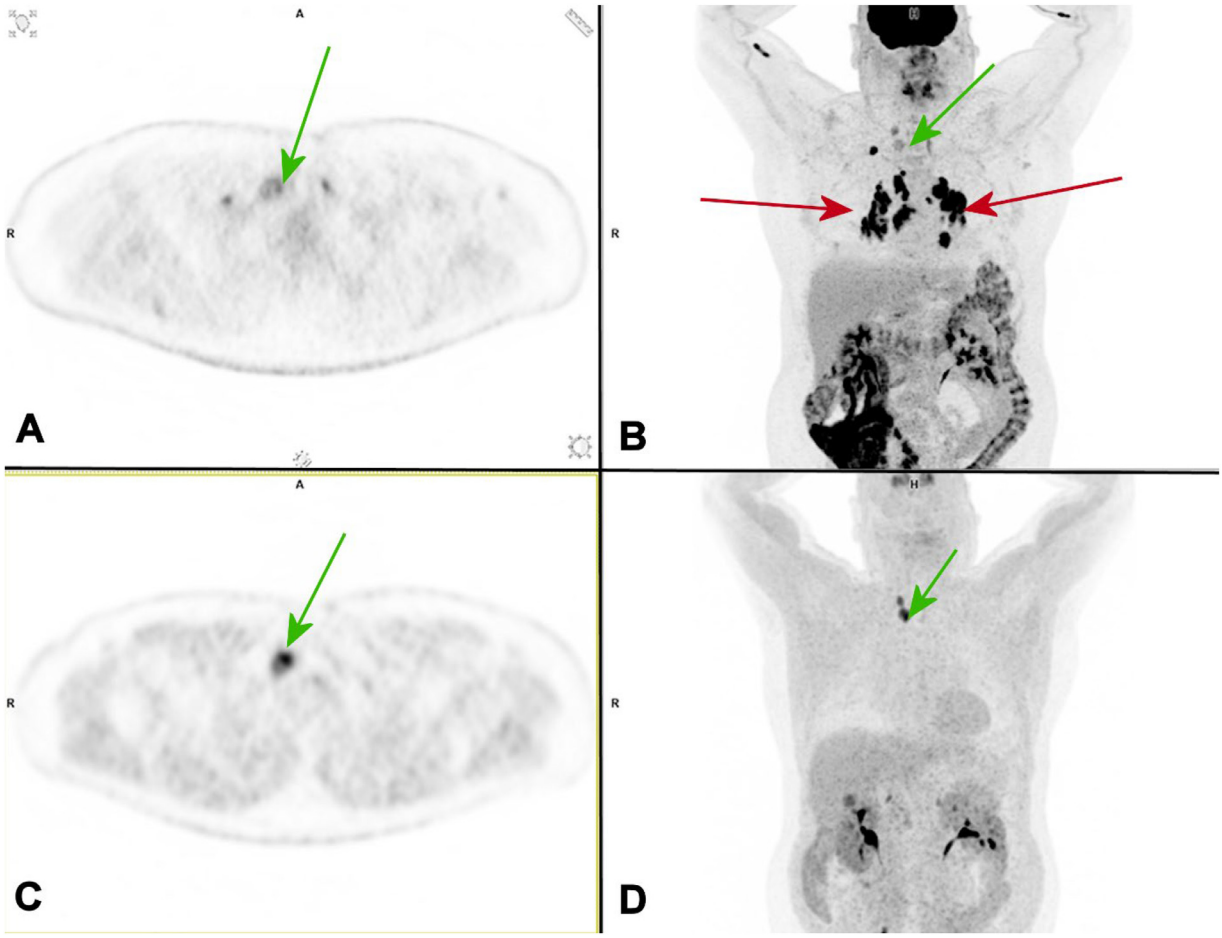

Figure 2 A 65 year old patient with known medullary thyroid carcinoma was scanned using [^{18}F]FDOPA (C, D) for the differentiation of enlarged mediastinal and hilar lymph nodes as previously seen on CT (not shown). While increased uptake was noted in lymph nodes in the lower neck area on the right (D, green arrow), this was not the case in the mediastinal lymph nodes. An [^{18}F]FDG PET scan was performed for further investigation and showed feint uptake in the lower right neck area (A, B, green arrow), but intense uptake in the mediastinal and hilar lymph nodes. Pathologic examination of these lymph nodes showed a granulomatous inflammation, considered to be due to sarcoidosis.

to imaging does not bring any additional benefits.[36] For the imaging procedure itself, anesthesia is required, with careful monitoring of vital signs and plasma glucose. Image reconstruction at different time points may allow optimal detection of focal lesions and recognition of physiological uptake patterns (Fig. 3).[37]

Neurology

Highest cerebral uptake of [^{18}F]FDOPA is usually present in the striatum where it is taken up through the LAT and converted to [^{18}F]fluorodopamine by L-DOPA decarboxylase in the presynaptic dopaminergic neurons. As with imaging of NETs the availability of [^{18}F]FDOPA in the striatum can be increased by premedication with carbidopa, which inhibits the peripheral action of AADC. [^{18}F]FDOPA is approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the detection of a presynaptic dopaminergic deficit in Parkinsonian syndromes, a group of neurodegenerative movement disorders characterized by symptoms of bradykinesia, rigidity, and/or rest tremor, of which idiopathic Parkinson's disease (IPD) is the most common.[38] IPD is characterized by neuronal loss of dopaminergic neurons in the substantia nigra, a small brain region in the midbrain, that project to the striatum.[39] Other etiologies that are marked by a presynaptic loss of striatal dopaminergic neurons include Dementia with Lewy bodies (DLB), multisystem atrophy (MSA) or tauopathies such as corticobasal degeneration CBD and progressive supranuclear palsy (PSP). Non-neurodegenerative etiologies of these symptoms include essential tremors, vascular parkinsonism, psychogenic parkinsonism and drug-induced parkinsonism. According to the combined European Association of Nuclear Medicine/SNMMI guidelines, presynaptic dopaminergic imaging can be performed to confirm the presence of a presynaptic degenerative dopaminergic deficit, which helps to differentiate between neurodegenerative and non-neurodegenerative etiologies of parkinsonism, in the differential diagnosis of DLB and Alzheimer's disease, and confirmation of diagnosis

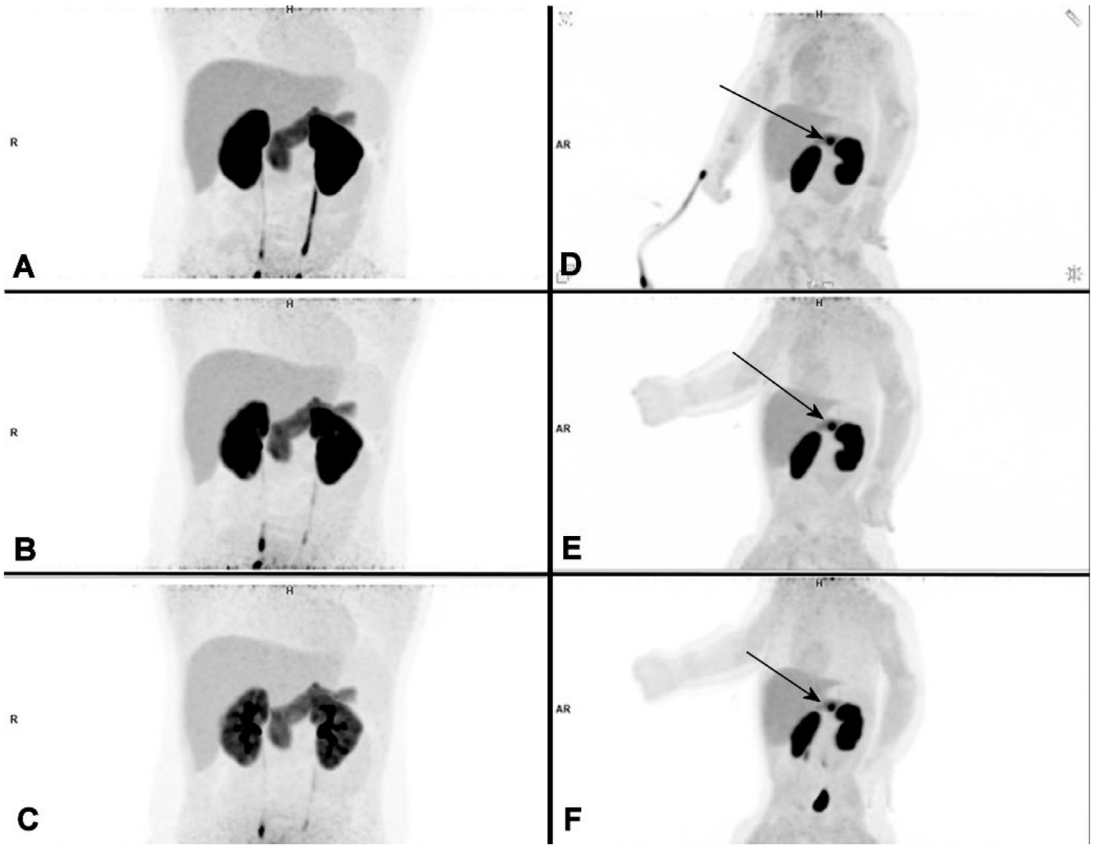

Figure 3 Two subjects scanned for differentiation between the focal and diffuse form of congenital hyperinsulinism using [18F]FDOPA PET. Images were acquired after 20 minutes (A, D), 40 minutes (B, E) and 60 minutes (C, F). On the left side, the Maximum Intensity Projection (MIP) images show the diffuse form, whereas on the right side a focal lesion (arrow) in the pancreatic body can be appreciated, slightly more visible on the latest image time point.

in early disease stages when symptoms may be subtle.[2] Figure 4 shows a typical example of a clinical scenario in which presynaptic dopaminergic imaging is requested.

When compared to dopamine transporter (DAT) SPECT, a more widely available method to assess presynaptic dopaminergic integrity, [18F]FDOPA PET offers comparable sensitivity and specificity, while providing the added advantage of higher spatial resolution, potential for quantitative analysis, and reduced susceptibility to the effects of normal aging.[40] On the other hand, the effect of dopaminergic degeneration may be smaller using [18F]FDOPA, presumably related to possible upregulation of the AADC enzyme as a compensatory mechanisms in the early stages of IPD.[41]

Image interpretation in the clinic usually consists of visual analysis and comparison of semi-quantificative values to a normal database. For semi-quantification, the striatal-to-occipital ratio (SOR) of static imaging is often used, as the specific signal of the occipital cortex is low due to little decarboxylase activity, and has been proven equally effective in differentiating IPD patients from healthy individuals as dynamic imaging.[42] Dynamic imaging can provide additional parameters such as the influx constant Ki, which could provide a more direct measure of the [18F]FDOPA influx constant. Full kinetic modeling of [18F]FDOPA is difficult because of metabolites, which may be partially suppressed by Carbidopa and Entacapone, but other metabolites such as 6-FDA may be present and complicate the analysis. Age related effects that influence SORs have not been consistently reported, yet a larger automated analysis of 892 [18F]FDOPA PET scans did show an age effect of striatal dopamine synthesis capacity.[43]

Although changes in cerebral [18F]FDOPA uptake in IPD are most prominent in the striatum, some studies have reported significant alterations outside this region, especially in frontal brain regions and motor cortex.[44-46] However, contrasting results have been found and sample sizes were small, limiting the generalizability of their findings. When interpreting extrastriatal [18F]FDOPA PET findings, it is important to note that this tracer is not only specific to dopaminergic neurons, but is also trapped by other neurons that express the AADC enzyme, including serotonergic and noradrenergic neurons.[47]

By the time a patient with IPD develops the typical motor symptoms, it is estimated that 50-60% of the dopaminergic neurons in the striatum have already been lost.[48] Nonmotor symptoms like idiopathic REM behavior disorder (iRBD), constipation, hyposmia, depression, and fatigue often precede IPD, marking a prodromal stage.[49] On their own, these symptoms lack sufficient sensitivity for screening,[50] but combined with dopaminergic imaging they could assist in

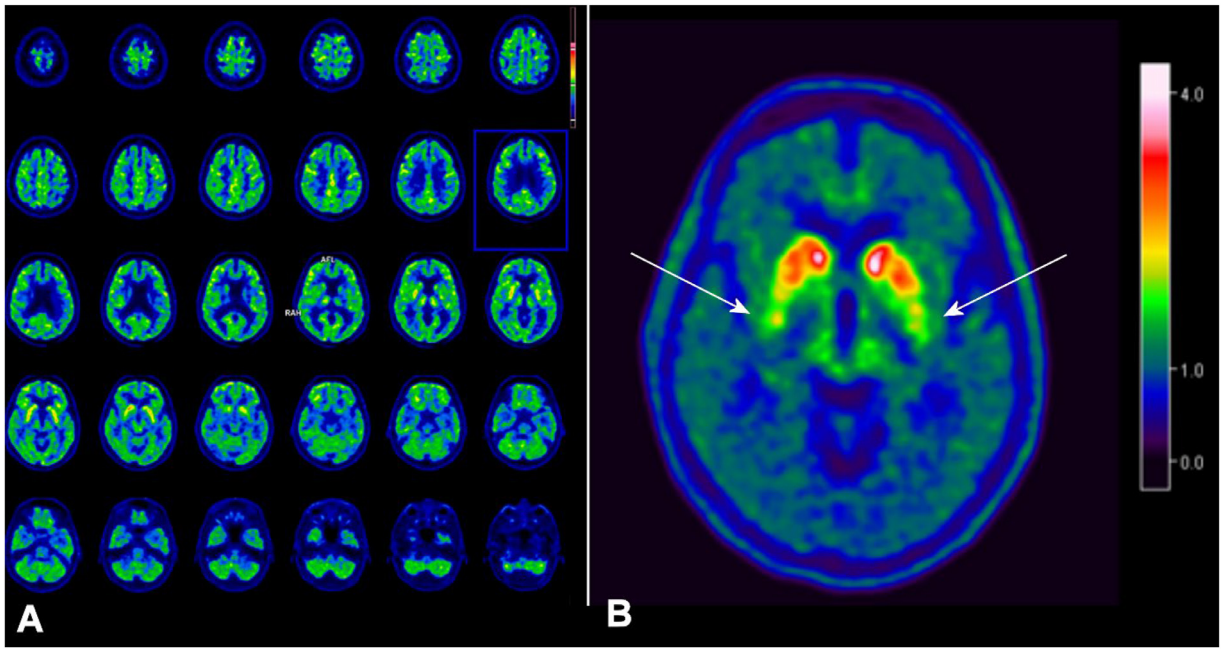

Figure 4 A 75 year old male patient was referred to the nuclear medicine department for an [^{18}F] FDG PET scan because of the suspicion of MSA. The patient presented with parkinsonism, autonomic dysfunction and had a poor response to treatment with L-DOPA. The [^{18}F]FDG PET scan (A) showed normal to slightly prominent uptake in the striatum, ruling against MSA. A subsequent [^{18}F]FDOPA scan (B) showed reduced striatal-to-occipital binding in the posterior putamen on both sides (arrows), fitting the diagnosis of idiopathic Parkinson's disease.

detecting a high-risk population.[51] Among the prodromal IPD symptoms, iRBD has been the most studied, as it is considered to be the first prodromal condition that may appear a decade prior to motor symptoms.[52] Recent studies have shown that patients with iRBD already show lower striatal [^{18}F]FDOPA uptake compared to healthy individuals, but longitudinal studies of this patient population with [^{18}F] FDOPA PET are scarce.[53]

[^{18}F]FDOPA PET is also a valuable tool for the investigation of PD subtypes and its progression. Early longitudinal studies reveal a consistent annual reduction of striatal [^{18}F] FDOPA uptake of 5-13% per year in patients with idiopathic Parkinson's disease.[54,55] The rate of dopaminergic decline varies, with the most prominent decline being present in the early stages of the disease.[54] The decline preferentially starts in the posterior putamen, followed by the anterior putamen and the caudate nucleus.

IPD is a highly heterogeneous disorder, with a wide range of motor and nonmotor symptoms.[56] The variability in clinical presentation suggests that different subtypes of IPD exist. Dopaminergic imaging through [^{18}F]FDOPA PET could help reveal differences in these clinical phenotypes and their relation to dopaminergic function. Multiple studies have established a link between presynaptic dopamine tracer uptake in the striatum, and especially in the putamen, and the severity of bradykinesia and rigidity, but not with tremor.[57,58] The latter is thought to be influenced more by serotonergic, rather than dopaminergic innervation.[58] However, significant heterogeneity exists across studies in sample size, stages of the disease and imaging acquisition techniques, with variations in varying or even absent correlations.[59] Furthermore, a recent study employing trimodal imaging with [^{18}F] FDOPA PET, [^{18}F]FDG PET and functional MRI has revealed that dopamine depletion in the putamen disrupts striatocortical connectivity, affecting motor control, and is associated with reduced functional connectivity between the striatum and sensorimotor cortex, as well as cortical hypometabolism, which correlates with motor impairments.[60] Beyond motor symptoms, reduced [^{18}F]FDOPA tracer uptake in the caudate has been associated with cognitive decline, especially in executive functioning.[61,62] Additionally, deficits in attention, visual memory, and verbal fluency have also been related to lower caudate dopamine activity.[63,64] A study with voxel-based analysis of whole-brain [^{18}F]FDOPA scans in 15 early-stage IPD patients found correlations between worse executive functioning and dopaminergic denervation in the anterior cingulate cortex and middle frontal gyrus, and verbal fluency and decreased tracer uptake in the dorsolateral prefrontal cortex and the striatum.[65] These findings underscores the role of the mesocortical dopaminergic pathways in cognitive function in early IPD.

Research into gender differences in brain [^{18}F]FDOPA uptake remains relatively limited, though some studies have indicated that women with IPD may show higher tracer uptake in certain brain regions compared to men. Kaasinen and colleagues have reported that women with IPD demonstrate increased uptake in the dorsolateral prefrontal cortex[45] and in a later study Kaasinen et al. observed that women had higher uptake in the putamen, ipsilateral to the predominant motor symptoms.[66] These studies were however limited due

to small sample sizes and lack of longitudinal data. Recent studies in non-PD populations support these gender differences. A study involving brain [^{18}F]FDOPA PET scans of 177 subjects with neuro-endocrine tumors also identified higher [^{18}F]FDOPA uptake in women, particularly in the putamen and diffuse cortical regions.[67] Similarly a retrospective analysis of [^{18}F]FDOPA PET scans of 115 subjects found that women exhibited higher striatal [^{18}F]FDOPA Ki values compared to men. However, no significant gender differences were observed in the striatal [^{18}F]FDOPA SOR.[43] These studies support the idea that striatal dopaminergic levels and connectivity are better preserved in women than in men, possibly related to a protective role of estrogens.[68]

In Parkinson's disease, 'brain first' versus 'gut first' etiopathogenesis subtypes have been described.[69] In the latter scenario, the alfa-synucleinopathy primary originates in the enteric or peripheral autonomic nervous system and then spreads to the brain.

Horsager and colleagues described typical imaging findings, depending on the subtype. The 'body-first' subtype is associated with a primary loss of cardiac MIBG signal and delayed colon transit time, followed by decreased striatal [^{18}F]FDOPA uptake, whereas the 'brain-first' subtype is characterized by an initial reduction of striatal [^{18}F]FDOPA uptake, followed by loss of cardiac MIBG signal and delayed colon transit time.[70] Interestingly, efforts have been undertaken to quantify sympathethic cardiac functioning in IPD patients with [^{18}F]FDOPA, initially with promising results. Goyal et al. showed significantly reduced cardiac uptake in PD patients with autonomic dysfunction (n = 28) in comparison with controls (n = 22).[71] However, a direct comparison of cardiac [^{18}F]FDOPA uptake with the validated cardiac innervation PET tracer [^{18}F]dopamine showed that [^{18}F]FDOPA was not able to distinguish between those patients that hat high or low cardiac uptake of [^{18}F]dopamine, making it questionable that it is indeed a valid sympathetic cardiac imaging agent.[72]

Another approach of investigating brain-body interactions, such as the gut-brain axis, is the simultaneous dynamic acquisitions of multiple regions using multiple tracers and a Large Axial Field of View (LAFOV) PET system. One such combination is the simultaneous assessment of the dopaminergic system of the brain and parasympathetic innervation of the intestines by using a dual tracer approach with the injection of [^{18}F]FDOPA and [^{11}C]donepezil. Several methods have been developed to distinguish between the signal of two different PET tracers.[73] As an alternative to simultaneous dual tracer PET imaging, the increased sensitivity of the LAFOV PET camera could allow administration of lower doses of radioactivity, limiting the time needed between injection of two separate radioligands.

Neuro-Oncology

Radiolabelled amino acids, such as ^{11}C-methionine ([^{11}C]MET, ^{18}F-fluoroethyl-L-tyrosine ([^{18}F]FET), or [^{18}F]F-DOPA, commonly show high uptake in glioma cells and metastases due to the overexpression of L-amino acid transporters with a high tumor to normal-ratio due to low uptake in the normal brain. Amino acid imaging may provide information relevant for treatment planning, assessment of treatment response and to discriminate between recurrent disease and treatment related changes ("pseudoprogression"). Its role is complementary as MRI is the primary imaging modality in all stages and may increase with the development of novel therapies such as immunotherapy.[74] Contrast enhancement on MRI can also occur due to the disruption of the blood-brain barrier by therapeutic agents, making conventional MRI unreliable to differentiate tumor progression from treatment related changes of gliomas.[75] In 2019, combined EANM/EANO/RANO guidelines were released with specific recommendations for imaging protocols and image analysis.[76] As opposed to [^{11}C]MET and [^{18}F]FET, semi-quantification of tumorratios relative to the contralateral striatum have also been used for [^{18}F]FDOPA. For detecting recurrent glioblastoma for instance, a threshold of 2.1 for the tumor-to-striatum$_{max}$ ratio has been proposed.[77] Several cut-off values have been proposed for [18F]FDOPA for primary diagnosis, differentiating high grade vs low grade glioma and defining tumor extent, for which the reader is referred to a systematic review.[78] Although [^{18}F]FDG PET is the most often used tracer in oncologic imaging, it is less sensitive in detecting primary or recurrent gliomas due to the physiologically high uptake of [^{18}F]FDG in the brain.[79] Upon visual assessment, amino acid tracers such as [^{18}F]FET, [^{11}C]MET and [^{18}F]FDOPA seem to perform equally well to identify primary brain tumors.[80] The use of [^{11}C]methionine however may be more limited due to its half-life of 20 minutes and the subsequent need of an on-site cyclotron.

In general there seems to be a positive correlation between amino acid uptake and tumor grade, probably related to increasing LAT1 expression,[81–83] but this has not consistently been shown in recurrent disease.[84] For tumor delineation, a recent systematic review described that in many studies discrepancies were present between [^{18}F]FDOPA derived biological tumor volume and those derived from MRI (contrast enhancement, perfusion), although it is not fully clear whether incorporation of additional [^{18}F]FDOPA derived information can improve outcome.[78] The sensitivity and specificity [^{18}F]FDOPA to differentiate between tumor progression and treatment related changes is estimated to be around 85-100% and 72-100% respectively, although most studies evaluating amino acid imaging for this indication used [^{18}F]FET PET.[85] In the postoperative setting, mild uptake of [^{18}F]FDOPA can be present at the margins of surgical resection, possibly due to macrophage activity.[78] Recently, radiomics have been utilized to predict significant molecular parameters in newly diagnosed gliomas using [^{18}F]FDOPA by means of machine learning. Zaragori et al., reported the best model reaching an AUC of 0.83 to predict the presence of isocitrate dehydrogenase (IDH) mutations.[86] Predictions using machine learning models may further improve by incorporating MRI based features.[87] [^{18}]FDOPA has also been used to identify responders in treatment response evaluation and was shown to be able to predict a

favorable response to antiangiogenic therapy such as bevacicumab[88]

Radiochemistry

A potential challenge for widely adopting [^{18}F]FDOPA in the clinic is the relatively high tracer production costs and the use of complex synthesis modules. [^{18}F]FDOPA can be prepared by electrophylic fluorination of the trimethylstannyl precursor with [^{18}F]fluorine gas ([^{18}F]F_2).[89] Activity yield and molar activity can be increased by producing [^{18}F]F_2 from [^{18}O]O_2 via a double-shoot approach instead of by the bombardment of ^{20}Ne using deuterons.[89] Nowadays, nucleophilic production methods have become available that rely on no-carrier added fluorine-18 instead of [^{18}F]F_2, resulting in an even higher molar activity and radiochemical yield, along with the potential benefit of safer synthesis.[90] Recently, a novel automated GMP compliant synthesis method of [^{18}F]FDOPA has been described, increasing the robustness of the production.[6] Cost saving can further be achieved by clustering single batch-production and patients on 1 day.[91] Interestingly, the first in human use of [^{18}F]FDOPA produced by organo-photoredox reactions has also recently been published.[92]

Future Perspectives

Aside from the widespread current applications in both clinic and research, technical advancements may further increase the utility of [^{18}F]FDOPA PET. For instance, novel LAFOV PET camera's with markedly increased sensitivities allow for significant dose reductions with regard to the scanning of children with CHI, whereas a more robust automated synthesis of [^{18}F]FDOPA may increase patient safety in this group. The increased camera sensitivity may also be used to detect smaller metastases in the context of MTC, especially lymph nodes in the central neck area and small lung nodules, which could support its role in primary staging. With respect to gastrointestinal NETs, it is increasingly being recognized that [^{18}F]FDOPA has increased sensitivity on a lesion basis, which could set this modality apart when considering curative surgery. For IPD and other parkinsonian syndromes, [^{18}F]FDOPA may help further defining subtypes of these heterogenous disorders by assessing presynaptic dopaminergic functioning. In addition, with LAFOV PET systems advancements can be achieved when performing noninvasive dynamic [^{18}F]FDOPA imaging, as the image derived input function can be obtained by sampling larger blood pools over the thorax.[93] This approach allows a more extensive quantification and could potentially be valuable in tracking disease progression and treatment response, which is not a common indication in clinical practice, but may be of relevance in future clinical trials evaluating disease modifying agents. With the advent of PET/MRI, simultaneous measurement of PET and MRI parameters during tasks could be performed, providing more accurate assessments of underlying biological processes.[94] Finally, amino acid imaging such as [^{18}F]FDOPA has been proven to be a valuable adjunct to MRI for differentiating radionecrosis from recurrent disease, and future research may shed more light on associated clinical benefits (e.g. reductions of unnecessary biopsies, treatment or follow-up imaging, improved quality of life).

Conclusions

Several decades after the introduction of [^{18}F]FDOPA PET, its role has become increasingly pivotal in the diagnosis and management of a broad spectrum of diseases. Given the complexity of neuroendocrine tumors, the guided selection of patients suited for specific imaging modalities by genotyping or biomarkers can further increase the diagnostic accuracy, as reflected by multiple guidelines. In addition, [^{18}F]FDOPA PET is well-established in the management of congenital hyperinsulism, parkinsonian syndromes and several domains in neuro-oncology. Although the widespread use of [^{18}F]FDOPA has been hampered by complex synthesis methods and high production costs in the past, significant efforts have been undertaken to provide robust GMP compliant synthesis methods with high activity yield and molar activity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Gilles N. Stormezand: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Eline de Meyer:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Klaas Pieter Koopmans:** Methodology, Writing – original draft. **Adrienne H. Brouwers:** Methodology, Writing – original draft, Writing – review & editing. **G. Luurtsema:** Conceptualization, Writing – original draft, Writing – review & editing. **Rudi A.J.O. Dierckx:** Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

References

1. Garnett ES, Firnau G, Nahmias C: Dopamine visualized in the basal ganglia of living man. Nature 305:137-138, 1983
2. Morbelli S, Esposito G, Arbizu J, et al: EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 1.0. Eur J Nucl Med Mol Imaging 47:1885-1912, 2020
3. Bozkurt MF, Virgolini I, Balogova S, et al: Guideline for PET/CT imaging of neuroendocrine neoplasms with (68)Ga-DOTA-conjugated

somatostatin receptor targeting peptides and (18)F-DOPA. Eur J Nucl Med Mol Imaging 44:1588-1601, 2017
4. De Leon DD, Arnoux JB, Banerjee I, et al: International guidelines for the diagnosis and management of hyperinsulinism. Horm Res Paediatr 97:279-298, 2024
5. Law I, Albert NL, Arbizu J, et al: Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [18F]FDG: Version 1.0. Eur J Nucl Med Mol Imaging 46:540-557, 2019
6. Luurtsema G, Kwizera C, Blok SN. et al. One-pot synthesis of 6-l-[18f] fluoro-3,4-dihydroxyphenylalanine (6-l-[18f] fdopa). (2024). (Patent No. WO2024058665)
7. Rindi G, Mete O, Uccella S, et al: Overview of the 2022 WHO classification of neuroendocrine neoplasms. Endocr Pathol 33:115-154, 2022
8. Nicoletti A, Baschi R, Cicero CE, et al: Sex and gender differences in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis: A narrative review. Mech Ageing Dev 212:111821, 2023
9. Gavriilidis P, Koole M, Annunziata S, et al: Positron range corrections and denoising techniques for Gallium-68 PET imaging: A literature review. Diagnostics 12:2335, 2022
10. Pauwels E, Cleeren F, Tshibangu T, et al: 18F-AlF-NOTA-octreotide outperforms 68Ga-DOTA-TATE/-NOC PET in neuroendocrine tumor patients: results from a prospective, multicenter study. J Nucl Med 64:632-638, 2022
11. Xoise Montravers F, Grahek D, et al: Can fluorodihydroxyphenylalanine PET replace somatostatin receptor scintigraphy in patients with digestive endocrine tumors? J Nucl Med 47:1455-1462, 2006
12. Balogova, S. et al. 18F-Fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. doi:10.1007/s00259-013-2342-x.
13. Berends AMA, Kerstens MN, Bolt JW, et al: False-positive findings on 6-[18F]fluor-l-3,4-dihydroxyphenylalanine PET (18F-FDOPA-PET) performed for imaging of neuroendocrine tumors. Eur J Endocrinol 179:125-133, 2018.. https://doi.org/10.1530/EJE-18-0321. Epub 2018 Jun 6. PMID: 29875288
14. Lloyd RV, Osamura RY, Klöppel G, et al: WHO Classification of Tumours of Endocrine Organs. International Agency for Research on Cancer, 2017
15. Tepede AA, Welch J, Lee M, et al: 18F-FDOPA PET/CT accurately identifies MEN1-associated pheochromocytoma. Endocrinol Diabetes Metab Case Rep 2020:19-0156, 2020.. https://doi.org/10.1530/EDM-19-0156. Epub ahead of print. PMID: 32130200; PMCID: PMC7077596
16. Iversen P, Kramer S, Ebbehoj A, et al: [18F]FDOPA PET/CT is superior to [68Ga]DOTATOC PET/CT in diagnostic imaging of pheochromocytoma. EJNMMI Res 13:108, 2023. https://doi.org/10.1186/s13550-023-01056-4. PMID: 38110755; PMCID: PMC10728412
17. Taïeb D, Hicks RJ, Hindié E, et al: European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging 46:2112-2137, 2019
18. Leimbach RD, Hoang TD, Shakir MKM: Diagnostic challenges of medullary thyroid carcinoma. Oncology 99:422-432, 2021
19. Cabanillas ME, McFadden DG, Durante C: Thyroid cancer. Lancet 388:2783-2795, 2016
20. Treglia G, Rufini V, Piccardo A, et al: Update on management of medullary thyroid carcinoma: Focus on nuclear medicine. Semin Nucl Med 53:481-489, 2023. https://doi.org/10.1053/j.semnuclmed.2023.01.003
21. Brammen L, Niederle MB, Riss P, et al: Medullary Thyroid Carcinoma: Do Ultrasonography and F-DOPA-PET-CT Influence the Initial Surgical Strategy? Ann Surg Oncol 25:3919-3927, 2018.. https://doi.org/10.1245/s10434-018-6829-3. Epub 2018 Oct 10. PMID: 30306375; PMCID: PMC6245031
22. Giovanella L, Treglia G, Iakovou I, et al: EANM practice guideline for PET/CT imaging in medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging 47:61-77, 2020
23. Wells SA, Asa SL, Dralle H, et al: Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 25:567-610, 2015
24. Treglia G, Villani MF, Giordano A, et al: Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 fluorodeoxyglucose positron emission tomography: A meta-analysis. Endocrine 42:535-545, 2012
25. Caobelli F, Chiaravalloti A, Evangelista L, et al: Predictive and prognostic value of 18F-DOPA PET/CT in patients affected by recurrent medullary carcinoma of the thyroid. Ann Nucl Med 32:7-15, 2018
26. Li P, Zhang Y, Xu T, et al: Sensitivities evaluation of five radiopharmaceuticals in four common medullary thyroid carcinoma metastatic sites on PET/CT: a network meta-analysis and systematic review. Nucl Med Commun 44:1114, 2023
27. Slavikova K, Montravers F, Treglia G, et al: What is currently the best radiopharmaceutical for the hybrid PET/CT detection of recurrent medullary thyroid carcinoma? Curr Radiopharm 6:96-105, 2013
28. Maggard MA, O'Connell JB, Ko CY: Updated population-based review of carcinoid tumors. Ann Surg 240:117-122, 2004
29. Nussbaum DP, Speicher PJ, Gulack BC, et al: Management of 1- to 2-cm carcinoid tumors of the appendix: Using the national cancer data base to address controversies in general surgery. J Am Coll Surg 220:894-903, 2015
30. Capdevila J, Chiaravalloti A, Evangelista L, et al: Molecular biology of neuroendocrine tumors: from pathways to biomarkers and targets. Cancer Metastasis Rev 33:345-351, 2014
31. Piccardo A, Fiz F, Bottoni G, et al: Head-to-head comparison between 18 F-DOPA PET/CT and 68 Ga-DOTA peptides PET/CT in detecting intestinal neuroendocrine tumours: A systematic review and meta-analysis. Clin Endocrinol (Oxf) 95:595-605, 2021
32. Ansquer C, Touchefeu Y, Faivre-Chauvet A, et al: Head-to-head comparison of 18F-DOPA PET/CT and 68Ga-DOTANOC PET/CT in patients with midgut neuroendocrine tumors. Clin Nucl Med 46:181-186, 2021
33. Palladino AA, Bennett MJ, Stanley CA: Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. Clin Chem 54:256-263, 2008. https://doi.org/10.1373/clinchem.2007.098988. Epub 2007 Dec 21. PMID: 18156285
34. Adzick NS, De Leon DD, States LJ, et al: Surgical treatment of congenital hyperinsulinism: Results from 500 pancreatectomies in neonates and children. J Pediatr Surg 54:27-32, 2019. https://doi.org/10.1016/j.jpedsurg.2018.10.030. Epub 2018 Oct 5. PMID: 30343978; PMCID: PMC6339589
35. Han B, Newbould M, Batra G, et al: Enhanced islet cell nucleomegaly defines diffuse congenital hyperinsulinism in infancy but not other forms of the disease. Am J Clin Pathol 145:757, 2016
36. States LJ, Christopher Davis J, Hamel SM, et al: 18F-6-Fluoro-L-Dopa PET/CT imaging of congenital hyperinsulinism. J Nucl Med 62:51S-56S, 2021
37. Navarathna N, Dalal D, Becker S, et al: 18F-FDOPA PET imaging in congenital hyperinsulinism for localization of a focal pancreatic lesion: Do medications interfere with radiotracer uptake? J Nucl Med 63:2388, 2022
38. States LJ, Becker SA, De León DD: Congenital hyperinsulinism: localization of a focal lesion with 18F-FDOPA positron emission tomography. Pediatr Radiol 52:693-701, 2022. https://doi.org/10.1007/s00247-021-05206-5
39. Postuma RB, Berg D, Stern M, et al: MDS clinical diagnostic criteria for Parkinson's disease. Movement Disorders 30:1591-1601, 2015
40. Morris HR, Spillantini MG, Sue CM, et al: The pathogenesis of Parkinson's disease. Lancet 403:293-304, 2024
41. Sawle GV, Colebatch JG, Shah A, et al: Striatal function in normal aging: implications for Parkinson's disease. Ann Neurol 28:799-804, 1990
42. Ribeiro MJ, Vidailhet M, Loc'h C, et al: Dopaminergic function and dopamine transporter binding assessed with positron emission tomography in Parkinson disease. Arch Neurol 59:580-586, 2002
43. Jokinen P, Helenius H, Rauhala E, et al: Simple ratio analysis of 18F-fluorodopa uptake in striatal subregions separates patients with early Parkinson disease from healthy controls. J Nucl Med 50:893-899, 2009
44. Nordio G, Easmin R, Giacomel A, et al: An automatic analysis framework for FDOPA PET neuroimaging. J Cereb Blood Flow Metabol 43:1285-1300, 2023

45. Rakshi JS, Uema T, Ito K, et al: Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [18F] dopa-PET study. Brain 122:1637-1650, 1999
46. Kaasinen V, Nurmi E, Brück A, et al: Increased frontal [18F]fluorodopa uptake in early Parkinson's disease: Sex differences in the prefrontal cortex. Brain 124:1125-1130, 2001
47. Cropley VL, Fujita M, Bara-Jimenez W, et al: Pre- and post-synaptic dopamine imaging and its relation with frontostriatal cognitive function in Parkinson disease: PET studies with [11C]NNC 112 and [18F] FDOPA. Psychiatry Res Neuroimaging 163:171-182, 2008
48. Pavese N, Rivero-Bosch M, Lewis SJ, et al: Progression of monoaminergic dysfunction in Parkinson's disease: A longitudinal 18F-dopa PET study. Neuroimage 56:1463-1468, 2011
49. Cheng HC, Ulane CM, Burke RE: Clinical progression in Parkinson disease and the neurobiology of axons. Ann Neurol 67:715-725, 2010
50. Berg D, Postuma RB, Adler CH, et al: MDS research criteria for prodromal Parkinson's disease. Movem Disord 30:1600-1611, 2015
51. de Klerk GW, van Laar T, Meles SK: A retrospective study of the MDS criteria for prodromal Parkinson's disease in the general population. NPJ Parkinson's Dis 10:1-7, 2024
52. Blokhin V, Pavlova EN, Katunina EA, et al: Dopamine synthesis in the nigrostriatal dopaminergic system in patients at risk of developing Parkinson's disease at the prodromal stage. J Clin Med 13:875, 2024
53. Hustad E, Aasly JO: Clinical and Imaging Markers of Prodromal Parkinson's Disease. Front Neurol 11:520289, 2020
54. Stokholm MG, Iranzo A, Østergaard K, et al: Assessment of neuroinflammation in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case-control study. Lancet Neurol 16:789-796, 2017
55. Morrish PK, Sawle GV, Brooks DJ: Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease. Brain 119(Pt 6):2097-2103, 1996
56. Nurmi E, Ruottinen HM, Bergman J, et al: Rate of progression in Parkinson's disease: A 6-[18F]fluoro-L-dopa PET study. Movement Disorders 16:608-615, 2001. https://doi.org/10.1002/mds.1139
57. Tolosa E, Garrido A, Scholz SW, et al: Challenges in the diagnosis of Parkinson's disease. Lancet Neurol 20:385-397, 2021
58. Scherfler C, et al: Correlation of dopaminergic terminal dysfunction and microstructural abnormalities of the basal ganglia and the olfactory tract in Parkinson's disease. Brain 136:3028-3037, 2013
59. Pikstra ARA, Van Der Hoorn A, Leenders KL, et al: Relation of 18-F-Dopa PET with hypokinesia-rigidity, tremor and freezing in Parkinson's disease. Neuroimage Clin 11:68-72, 2016
60. Sood A, Shukla J, Shree R, et al: Comparative performance of 99mTc-TRODAT-1 SPECT/CT and 18F-FDOPA PET/CT imaging in patients with Parkinson's disease, Parkinson-plus syndrome, and essential tremor. Clin Nucl Med 46:95-102, 2021
61. Ruppert MC, Greuel A, Tahmasian M, et al: Network degeneration in Parkinson's disease: multimodal imaging of nigro-striato-cortical dysfunction. Brain 143:944-959, 2020
62. Brück A, Portin R, Lindell A, et al: Positron emission tomography shows that impaired frontal lobe functioning in Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. Neurosci Lett 311:81-84, 2001
63. Brück A, Aalto S, Nurmi E, et al: Cortical 6-[18F]fluoro-L-dopa uptake and frontal cognitive functions in early Parkinson's disease. Neurobiol Aging 26:891-898, 2005
64. Jokinen P, et al: Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. Parkinsonism Relat Disord 15:88-93, 2009
65. Rinne JO, Portin R, Ruottinen H, et al: Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. Arch Neurol 57:470-475, 2000
66. Picco A, Morbelli S, Piccardo A, et al: Brain (18)F-DOPA PET and cognition in de novo Parkinson's disease. Eur J Nucl Med Mol Imaging 42:1062-1070, 2015
67. Kaasinen V, Maguire RP, Hundemer HP, et al: Corticostriatal covariance patterns of 6-[18F]fluoro-L-dopa and [18F]fluorodeoxyglucose PET in Parkinson's disease. J Neurol 253:340-348, 2006
68. Toch SR, Poussier S, Micard E, et al: Physiological whole-brain distribution of [18F]FDOPA uptake index in relation to age and gender: results from a voxel-based semi-quantitative analysis. Mol Imaging Biol 21:549-557, 2019
69. Borghammer P, Van Den Berge N: Brain-first versus gut-first Parkinson's disease: A hypothesis. J Parkinsons Dis 9:S281-S295, 2019
70. Horsager J, Andersen KB, Knudsen K, et al: Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. Brain 143:3077-3088, 2020
71. Goyal H, Sharma A, Sharma C, et al: Assessment of myocardial sympathetic innervation with 18F-FDOPA-PET/CT in patients with autonomic dysfunction: Feasibility study in IPD patients. J Nucl Cardiol 29:1280-1290, 2022
72. Goldstein DS, Holmes C: Is 18F-DOPA a valid cardiac sympathetic neuroimaging agent? Clin Auton Res 32:445-453, 2022
73. Zeng F, Fang J, Muhashi A, Liu H: Direct reconstruction for simultaneous dual-tracer PET imaging based on multi-task learning. EJNMMI Res 13:7, 2023. https://doi.org/10.1186/s13550-023-00955-w. PMID: 36719532; PMCID: PMC9889598
74. Okada H, Weller M, Huang R, et al: Immunotherapy response assessment in neuro-oncology: A report of the RANO working group. Lancet Oncol 16:e534-e542, 2015
75. Reddy K, Westerly D, Chen C: MRI patterns of T1 enhancing radiation necrosis versus tumour recurrence in high-grade gliomas. J Med Imaging Radiat Oncol 57:349-355, 2013
76. Law I, Albert NL, Arbizu J, et al: Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [18F]FDG: Version 1.0. Eur J Nucl Med Mol Imaging 46:540, 2019
77. Herrmann K, Czernin J, Cloughesy T, et al: Comparison of visual and semiquantitative analysis of 18F-FDOPA-PET/CT for recurrence detection in glioblastoma patients. Neuro Oncol 16:603-609, 2014. https://doi.org/10.1093/neuonc/not166. Epub 2013 Dec 4. PMID: 24305722; PMCID: PMC3956344
78. Somme F, Bender L, Namer IJ, et al: Usefulness of 18F-FDOPA PET for the management of primary brain tumors: a systematic review of the literature. Cancer Imag 20:1-13, 2020
79. Chen W, Silverman DH, Delaloye S, et al: 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy. J Nucl Med 47:904-911, 2006. PMID: 16741298
80. Kratochwil, C, Combs SE, Leotta K. et al. Both 18 F-fluorodihydroxyphenylalanine (18 F-DOPA) and 18 F-fluoroethyltyrosine. 18,
81. Youland RS, Kitange GJ, Peterson TE, et al: The role of LAT1 in 18F-DOPA uptake in malignant gliomas. J Neurooncol 111:11, 2013
82. Chiaravalloti A, Fiorentini A, Villani V, et al: Factors affecting ^{18}F FDOPA standardized uptake value in patients with primary brain tumors after treatment. Nucl Med Biol 42:355-359, 2015
83. Janvier L, Olivier P, Blonski M, et al: Correlation of SUV-derived indices with tumoral aggressiveness of gliomas in static 18F-FDOPA PET: Use in clinical practice. Clin Nucl Med 40:e429-e435, 2015
84. Fueger BJ, Czernin J, Cloughesy T, et al: Correlation of 6-18F-fluoro-L-dopa PET uptake with proliferation and tumor grade in newly diagnosed and recurrent gliomas. J Nucl Med 51:1532-1538, 2010
85. de Zwart PL, van Dijken BRJ, Holtman GA, et al: Diagnostic accuracy of PET tracers for the differentiation of tumor progression from treatment-related changes in high-grade glioma: A systematic review and meta-analysis. J Nucl Med 61:498-504, 2020
86. Zaragori T, Oster J, Roch V, et al: 18F-FDOPA PET for the noninvasive prediction of glioma molecular parameters: A radiomics study. J Nucl Med 21:27, 2022. https://doi.org/10.1186/s40644-021-00396-5. PMID: 33691798; PMCID: PMC7944911
87. Tatekawa H, Hagiwara A, Uetani H, et al: Differentiating IDH status in human gliomas using machine learning and multiparametric MR/PET. Cancer Imag 21:27, 2021.
88. Schwarzenberg J, Czernin J, Cloughesy TF, et al: Treatment response evaluation using 18 F-FDOPA PET in patients with recurrent malignant glioma on bevacizumab therapy. Clin Cancer Res 20:3550-3559, 2014

89. de Vries EFJ, Luurtsema G, Brussermann M, et al: Fully automated synthesis module for the high yield one-pot preparation of 6-[F-18]fluoro-L-DOPA. Radiat Isotopes 51:389-394, 1999
90. Neves ÂCB, Hrynchak I, Fonseca I, et al: Advances in the automated synthesis of 6-[18F]Fluoro-L-DOPA. EJNMMI Radiopharm Chem 6:1-19, 2021
91. Aboian M, Barajas R, Shatalov J, et al: Maximizing the use of batch production of 18F-FDOPA for imaging of brain tumors to increase availability of hybrid PET/MR imaging in clinical setting. Neurooncol Pract 8:91, 2021
92. Wang L, Lv Z, Yang L, et al: First-in-human evaluation of [18F]FDOPA produced by organo-photoredox reactions. Bioconjug Chem 35:1160-1165, 2024.. https://doi.org/10.1021/ACS.BIOCONJCHEM.4C00252. Epub 2024 Jul 18. PMID: 39023912
93. Reed MB, Handschuh PA, Schmidt C, et al: Validation of cardiac image-derived input functions for functional PET quantification. Eur J Nucl Med Mol Imaging 51:2625-2637, 2024
94. Shang S, Li D, Tian Y, et al: Hybrid PET-MRI for early detection of dopaminergic dysfunction and microstructural degradation involved in Parkinson's disease. Communicat Biol 4:1-9, 2021