The clinical value of [^{18}F]fluoro-dihydroxyphenylalanine positron emission tomography in primary diagnosis, staging, and restaging of neuroendocrine tumors

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Abstract

The study was set up to determine the clinical value of dihydroxyphenylalanine positron emission tomography-computed tomography ([^{18}F]DOPA PET-CT) in patients with neuroendocrine tumors (NETs). Eighty-two patients with suspected/known NET were imaged with PET(-CT) using [^{18}F]DOPA. Patients were divided into two groups: primary diagnosis/staging and restaging of disease. All patients without previous diagnosis of NET had biochemical proof of disease. The diagnostic accuracy of PET was assessed by comparing the histopathology and clinical follow-up. The overall accuracy of [^{18}F]DOPA PET was 90%. In patients having PET for primary diagnosis/staging ($n=32$), the accuracy of PET was 88%, and for restaging 92% ($n=61$). The mean s.d. sizes of primary and metastatic lesions detected by PET were 26 ± 11 and 16 ± 9 mm respectively. In organ-region-specific analysis, the sensitivity and specificity were 100% in the primary diagnosis of pheochromocytoma ($n=16$) and metastases were found in all cases with recurrent disease ($n=5$). The accuracy for NET of gastrointestinal tract was 92% in restaging ($n=24$). For the NETs located in the head–neck–thoracic region ($n=19$), the overall accuracy of PET was 89% including 12 cases of recurrent medullary thyroid cancer with a sensitivity of 90%. In analysis of patients with biochemical proof of disease combined with negative conventional imaging methods, PET had positive and negative predictive value of 92% and 95% respectively. [^{18}F]DOPA PET-CT provided important additional information in the diagnosis of pheochromocytoma and restaging of known NET. Both in primary diagnosis and in patients with formerly known NET and increasing tumor markers, [^{18}F]DOPA PET-CT is a sensitive first-line imaging method.

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of rare tumors arising from diffuse cells. These tumors are usually relatively slow growing with low malignant potential, but have functional characteristics

that can produce pronounced endocrine-related symptoms despite their small size. NETs are located mainly (90%) in the gastrointestinal tract and the pancreas (gastroenteropancreatic NETs). They can also be found in various other sites such as the bronchopulmonary

system, the adrenal medulla (pheochromocytoma), the extra-adrenal paraganglia (paraganglioma), and the head–neck region (e.g., neuroblastoma, medullary thyroid cancer (MTC)). The incidence of NETs (2/100 000 for men and 2.4/100 000 for women) is believed to be higher than reported, primarily due to the substantial number of undetected and misclassified tumors (Kloppel *et al.* 2007, Modlin *et al.* 2008).

Since surgery is the only curative approach in NET, early detection and accurate staging of the disease are essential to establish the treatment and prognosis of the disease. Several imaging modalities are available for patients with a suspected NET such as anatomical imaging by computed tomography (CT) and magnetic resonance imaging (MRI) combined with functional whole-body imaging by scintigraphy with labeled analogues of somatostatin (SRS) and metaiodobenzylguanidine (MIBG). In addition, several recent studies have shown the usefulness of positron emission tomography (PET) in detection, characterization, and staging of NETs.

PET supplies a range of labeled compounds to be used for the characterization of tumor biochemistry. However, the most common tracer in PET imaging, [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), is of limited value in the diagnosis of NETs except for aggressive form of disease (Jadvar & Segall 1997, Adams *et al.* 1998, Pasquali *et al.* 1998). In this context, different tracers have been proposed to visualize NETs and the majority of these experiments have been based on the NET's capacity to take up and decarboxylate amino acid precursors (APUDomas; Pearse 1969). For example, PET using radiolabeled amine precursors, such as hydroxytryptophan (HTP; Orlefors *et al.* 2005, Koopmans *et al.* 2008), hydroxyephedrine (Trampal *et al.* 2004), dopamine (Pacak *et al.* 2001), and dihydroxyphenylalanine (DOPA), has been developed for the localization of NETs. Since the pioneering study of Ahlstrom *et al.* (1995) using carbon-11-labeled-DOPA, a fluorine-18-labeled analogue [^{18}F]DOPA has been used for the diagnosis of carcinoid tumors (Hoegerle *et al.* 2001b, Becherer *et al.* 2004, Koopmans *et al.* 2008), pheochromocytomas (Hoegerle *et al.* 2002, Timmers *et al.* 2007a), insulinomas (Otonkoski *et al.* 2006, Kauhanen *et al.* 2007, Koopmans *et al.* 2008), medullary thyroid carcinomas (Hoegerle *et al.* 2001a), and glomus tumors (Hoegerle *et al.* 2003).

Despite the promising results of [^{18}F]DOPA PET imaging in the diagnosis of NETs, it is not yet commonly used in the present clinical practice. The main goal of the study was to determine the added clinical value of [^{18}F]DOPA PET in a group of patients

with different types of NET both in primary diagnosis and in staging and restaging of disease.

Subjects and methods

Subjects

We analyzed retrospectively the first 119 consecutive patients referred for [^{18}F]DOPA study to our national PET center between January 2000 and March 2007. Ten adult patients with surgically treated insulinoma and β -cell hyperplasia (Kauhanen *et al.* 2007), and 14 patients with CHI (congenital hyperinsulinism of infancy) (Otonkoski *et al.* 2006), have been reported before and were excluded from the analysis. Furthermore, ten additional patients, who underwent [^{18}F]DOPA PET for primary diagnosis and did not have biochemical proof of disease were excluded from the study. In three patients, complete data were not available, and therefore a total of 82 patients (37 males, 45 females, mean age: 40.5 ± 7.8 years) and 93 PET scans were included in the study. Depending on the indication for PET scanning, study patients were divided into 1) primary diagnosis and staging of disease and 2) restaging of disease. Ten of the study patients had a diagnosis of multiple endocrine neoplasia. The clinical characteristics, biochemical findings, reports of imaging studies, treatments, and follow-up examinations were recorded. The diagnostic accuracy of the PET studies was assessed by comparing the histopathological reports ($n=30$) and clinical follow-up (mean: 17.3 ± 11.9 months, $n=63$). Demographic data are given in Table 1. The data collection and analysis were approved by the Institutional Review Board.

[^{18}F]DOPA PET-CT and PET technique

Patients fasted for at least 6 h before the PET scan. If the patient was on medication that could affect the biodistribution of [^{18}F]DOPA (diazoxide, somatostatin analogues, or cortisone), the medication was withdrawn 24 h before the study. In patients with suspicion of a pancreaticoduodenal NET, plasma glucose level was monitored and a glucose (G5–G10%, 40–100 ml/h) infusion was given, if needed, to keep the plasma glucose between 4.0 and 5.0 mmol/l.

The [^{18}F]DOPA PET scans were acquired using PET-CT (Discovery PET-CT; General Electric Medical Systems, Milwaukee, WI, USA; $n=70$) and GE Advance (General Electric Medical Systems; $n=33$) scanners. [^{18}F]DOPA PET was synthesized according to previously described methods (Bergman *et al.* 1994). The average administered dose of

Table 1 Clinical features of patients studied by [¹⁸F]DOPA scan (*n*=93)

Sex (male/female)	37/45
Age	40.5 ± 7.8
Indication of PET scanning	
Primary diagnosis and staging (<i>n</i> =32)	
Biochemical proof and clinical NET symptoms	23
Biochemical proof without clinical NET symptoms	9
Restaging (<i>n</i> =61)	
F–U without biochemical proof	17
Standard F–U scan	8
Conventional imaging shows lesions	9
Biochemical proof and clinical NET symptoms	11
Biochemical proof without clinical NET symptoms	33
Chromogranin A nmol/l (<i>n</i> =68)	60.7 ± 157.9
Reference of final diagnosis	
Histology	30
F–U	63
Mean F–U time (months)	17.3 ± 11.9
Primary treatment modality after PET	
Surgery	30
Somatostatin analogues	11
Combined with chemo/radiation therapy	5
Chemoradiotherapy	4
Interferon-α	3
F–U without treatment	33
Other medical treatment	7

F–U, follow-up.

[¹⁸F]DOPA was 234 ± 56 MBq. The decarboxylase inhibitor, carbidopa, was given in 19 patients as a premedication. Scanning began 60 min after tracer injection. Patients underwent a whole-body PET scan from the level of the eyes to the mid-thigh with a GE Advanced PET scanner operated in 2D mode, and after May 2005, scans were acquired on a combined PET-CT. This CT-based scan was used for attenuation correction purposes and to help in anatomic localization of DOPA uptake. Immediately after the CT, an emission PET scan was acquired in 3D mode over the same anatomical regions starting at the level of the mid-thigh.

To obtain images for visual and semi-quantitative analysis, the data were corrected for dead time, decay and photon attenuation, and reconstructed in a 128 × 128 matrix. The final in-plane resolution in segmented attenuation correction and iterative-reconstructed (SAC-OSEM) and Hann-filtered (4.6 mm) image was 5 mm (full-width half-maximum (FWHM)) when scanned with GE Advance. A fully 3D ML-OS-EM reconstruction algorithm (VuePoint) was used when scanning with PET-CT. The images were reconstructed using two iterations and 28 subsets with a 6.0 mm FWHM post-filter.

PET images were analyzed visually and semi-quantitatively by calculating mean and maximum standardized uptake values (SUVs) defined as the ratio of activity per milliliter of tissue to the activity in the injected dose, corrected by decay and per patient's body weight in the region of interest (ROI). ROIs were placed around the regions of increased DOPA uptake for SUV_{max} and SUV_{mean} determination. Any focal tracer accumulation exceeding normal regional tracer uptake was interpreted as a pathological finding. Whenever PET-CT was available, a clear uptake in the area where CT suggested bone fracture or degenerative bone lesions was not regarded as a positive finding.

Other imaging studies

All concurrent available conventional imaging studies (CT, MRI, SRS, MIBG scintigraphy) before 12 months (mean: 4.4 months, range: 0.5–12 months) of the PET scan were reviewed and catalogued. A total of 98 morphological imaging studies was available for comparison. Anatomical imaging with CT was performed on 75 patients and MRI on 23 patients. Some patients received additional functional imaging with SRS (*n*=29) and [¹²³I]MIBG scintigraphy (*n*=5) during their clinical workup.

Data evaluation

The diagnostic accuracy of the PET studies was assessed by comparing the histopathological reports (*n*=30) and the imaging findings. When the histology was not available, the consensus was based on the sum of the imaging procedures and follow-up examinations (*n*=63). Primary tumor site and axis were taken from the pathology reports if the patient had been operated, and otherwise from imaging studies. All the regions and lesions seen by different imaging modalities were calculated. If the number of lesions was over 10, the number of lesions was truncated at 11 lesions to avoid the bias toward that region.

Statistical analysis

The results are expressed mainly as means ± s.d. The specificity and sensitivity of PET for NET detection were calculated using the pathology results and the clinical follow-up as a gold standard using a 2 × 2 contingency table. A Mc Nemar test was performed to compare PET and combined CT/MRI (*n*=83) and SRS/MIBG scintigraphy (*n*=35) results, and κ coefficient was determined to quantify agreement of these imaging methods. The Wilcoxon signed-rank test

was used to evaluate the number of regions and lesions diagnosed by different imaging modalities. Fisher’s exact test was used to test an association between symptoms and biochemical signs and PET findings. $P<0.05$ was considered statistically significant. All statistical analyses were performed with SAS (version 8.2; SAS, Cary, NC, USA).

Results

Clinical and endocrine status

Patients were divided into five different study groups depending on the indication of PET scanning (Table 1). In primary diagnosis and staging, only patients with biochemical proof of disease were included, instead in restaging of known NET also patients with negative biochemistry were included ($n=17$). The serum chromogranin A (CgA) levels were significantly increased in 87% of the study patients with a mean level of 60.7 nmol/l ($n=68$) (normal value: <4.0 nmol/l). However, the serum level of CgA was not related to the distribution of positive or negative [¹⁸F]DOPA PET findings ($P=0.10$). All the patients with primary suspicion of pheochromocytoma had elevated urinary metanephrine level with a mean value of 11.11 ± 15.28 μ mol/day (normal value: 0.1–1.4 μ mol/day), while normetanephrine values were normal (mean: 4.52 ± 3.65 μ mol/day, normal value: 0.5–4.2 μ mol) ($n=16$). In all patients with recurrent MTC, calcitonin or carcinoembryonic antigen (CEA) was increased. The mean calcitonin level was 1418 ± 1830 pmol/l ($n=13$) (normal value: <3.8 pmol/l for male, <1.7 pmol/l for female) and that of CEA was 186 ± 209 μ g/l ($n=11$; normal value: <5.0 μ g/l). Patients with suspicion of pancreaticoduodenal NET had a fasting mean glucose level of 4.3 ± 3.9 mmol/l (normal value: >2.5 mmol/l), with concomitant insulin of 100.8 ± 156.4 mU/l (normal value: 5–20 mU/l), and C-peptide of 2.31 ± 3.48 nmol/l (normal value: 0.33–0.83 nmol/l). In the cases of ectopic

ACTH syndrome, all patients had blunted suppression in 1 mg dexamethasone test (plasma cortisol: 1049 ± 480 nmol/l), and their serum ACTH concentration was 150 ± 221 ng/l (range: 29–640 ng/l). In restaging group, there was no significant association between the presence of symptoms and the biochemical proof of disease and sensitivity of [¹⁸F]DOPA PET ($P=0.18$ and 0.51 respectively).

[¹⁸F]DOPA PET and conventional imaging

The results of imaging modalities in different indications are shown in Table 2. In 44 patients, [¹⁸F]DOPA PET scans gave additional information compared with conventional imaging methods, and in another 11 patients PET gave information for the clinical diagnosis without conventional imaging methods. In addition, although 29 of the study patients had concordant findings in [¹⁸F]DOPA PET and conventional imaging, PET gave more detailed information in diagnostically obscure patients with atypical symptoms and biochemical suspicion of the disease.

Differences in classification between [¹⁸F]DOPA PET and combined CT/MRI and SRS/MIBG were statistically significant ($P=0.009$ and 0.003 respectively). The κ coefficient for agreement was negative ($\kappa=-0.078$) for [¹⁸F]DOPA PET and CT/MRI, and that for [¹⁸F]DOPA PET and SRS/MIBG scintigraphy was negligible ($\kappa=0.022$).

In the analysis of 31 patients with advanced stage of disease, [¹⁸F]DOPA PET detected significantly more affected regions (mean 2.7) and lesions (mean 5.0) compared with the combined results of CT and MRI (regions; mean 1.1, lesions; mean 1.7) ($P<0.001$). Additionally, [¹⁸F]DOPA PET detected a mean value of 0.9 regions and 1.9 lesions more than SRS and MIBG scintigraphy ($n=15$) (regions, 3.0 vs 2.1; lesions, 5.5 vs 3.6) (Fig. 1).

Table 2 Results of different imaging modalities

	Search for primary and staging ($n=32$)					Suspicion of recurrence ($n=51$)					Follow-up ($n=10$)				
	TP	TN	FP	FN	Total	TP	TN	FP	FN	Total	TP	TN	FP	FN	Total
[¹⁸ F]DOPA PET ($n=93$)	9	19	2	2	32	28	18	1	4	51	7	3	0	0	10
CT ($n=75$)	5	16	3	4	28	11	19	2	10	42	3	1	0	1	5
MRI ($n=23$)	3	6	0	1	10	5	4	3	0	12	1	0	0	0	1
SRS/MIBG ^a ($n=34$)	2	6	5	2	15	7	2	3	6	18	1	0	0	0	1

TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative.
^aFive patients with suspicion of pheochromocytoma underwent MIBG scintigraphy.

Figure 1 Representative case of the patient with additional findings in [¹⁸F]DOPA PET compared with SRS (OctreoScan). Patient had NET tumor of ileum operated 2 years before. At follow-up, diarrhea and mild increase in chromogranin appeared. (a) In SRS imaging, one suspected lesion was seen in liver (arrow). (b) [¹⁸F]DOPA PET (arrows) revealed three lesions. Patient was operated on and metastatic lesions from diaphragm and retroperitoneum were resected.

Patients with positive biochemistry and negative conventional imaging

Thirty-five patients had positive biochemistry and negative conventional imaging and 32 of these patients had true-positive or -negative findings in PET scanning. In this patient group, [¹⁸F]DOPA PET had positive and negative predictive value of 0.92 and 0.95 respectively. When only patients with histological verification of disease were analyzed, a PPV of 1.00 ($n=8$) and NPV of 0.67 ($n=3$) were achieved. A mean number of different conventional imaging tests per patient was 1.46 ± 0.67 before referral for the PET scan.

Primary diagnosis and staging of NET

The distribution of indications and [¹⁸F]DOPA PET scan results are shown in Fig. 2. The accuracy of [¹⁸F]DOPA PET was 87% in patients having PET imaging for the primary diagnosis and staging of a NET ($n=32$). The mean size of the primary tumors was 26 ± 11 mm. When assessing the organ-region-specific analysis, both the sensitivity and specificity for pheochromocytoma ($n=16$) were 100%. Four out of five primary pheochromocytomas were located in left adrenals, and one in both adrenals in addition to metastatic lymph node in aorta bifurcation was identified in [¹⁸F]DOPA PET. An accuracy of 50% was achieved in the localization of primary tumors of the GI tract when pancreaticoduodenal tumors were

excluded. Furthermore, the sensitivity and specificity in detecting primary pancreaticoduodenal NETs ($n=8$) were 67% and 60% respectively. In six patients, [¹⁸F]DOPA PET scan was done for suspicion of ectopic ACTH-producing tumors, producing one true-positive and five true-negative findings.

Restaging of NET

Overall, 61 patients had [¹⁸F]DOPA PET for restaging of disease. The indications for [¹⁸F]DOPA PET imaging of restaging included suspicion of recurrence ($n=51$) and follow-up studies ($n=10$; Fig. 2). The overall accuracy of [¹⁸F]DOPA PET for restaging was 92%. In this group, [¹⁸F]DOPA PET detected advanced stage of disease in 31 patients (Fig. 3), while in four patients, the PET scan failed to detect metastasis partly ($n=2$) or completely ($n=2$). In restaging of disease, the accuracy was 89% for pheochromocytoma ($n=9$) and 93% for a GI tract NET ($n=24$). Furthermore, in tumors located in the head-neck-thoracic region ($n=19$), the overall accuracy of [¹⁸F]DOPA PET was 89%, including 12 cases of recurrent MTC with a sensitivity and specificity of 90% and 100% respectively. The sizes of metastatic lesions were 16 ± 9 mm (range: 15–40 mm).

False-negative and false-positive findings

Overall, 9 out of 93 [¹⁸F]DOPA PET scans (10%) were considered either false negative ($n=6$) or false positive ($n=3$). In a subgroup analysis of six patients with false-negative finding in [¹⁸F]DOPA PET imaging, five out of six had advanced neuroendocrine carcinoma. In two of these patients, [¹⁸F]DOPA PET failed to show liver metastasis, and in one patient with metastasized NET, [¹⁸F]DOPA PET showed metastasis only in the mesenterium when CT showed additional lesions in the mediastinum and axillary regions, although histological verification of these lesions was missing. There were two additional patients where [¹⁸F]DOPA PET was not able to show metastasis in the neck region. Furthermore, only one benign form of NET, a 15 mm insulinoma in the head of the pancreas, was undetectable by [¹⁸F]DOPA PET.

In three cases, [¹⁸F]DOPA uptake in the PET scans was considered to be false positive. One patient with suspicion of paraganglioma recurrence had [¹⁸F]DOPA uptake in skeletal structures and in the right adrenal. Histological verification confirmed metastasis in the lumbar spine but a normal adrenal gland. One patient with strong suspicion of functional pancreatic NET had obscure diagnostic findings. He had two PET scans because of suspicion of insulinoma. Both the PET

Figure 2 Distribution of findings in PET scan in primary and secondary diagnostics *One patient with neuroblastoma. [†]12 PET scans in patients with medullary thyroid cancer, one patient with a NET in the neck region and two MEN-patients with hyperparathyreosis previously operated on. [‡]Three patients with a lung NET. TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative.

scans showed accumulation of [¹⁸F]DOPA in the head of the pancreas. The patient has been in follow-up with moderate symptoms for already 18 months since the second PET scan. Due to the lack of a histological diagnosis, the PET finding in this patient was considered a false-positive result.

Discussion

The present study indicates that [¹⁸F]DOPA PET is a useful functional approach for diagnostic imaging of NETs with an overall accuracy of 90%. For the primary diagnosis and staging of clinically suspected NET, the [¹⁸F]DOPA PET has an accuracy of 88% (n=32) and 92% for restaging of disease (n=61).

Furthermore, this retrospective series of 93 [¹⁸F]DOPA PET scans in 82 patients showed that [¹⁸F]DOPA PET imaging had an impact on the clinical management in 55 out of 93 (59%) cases and, additionally, confirmed the diagnosis in 29 obscure cases with inconclusive findings in conventional imaging. In a group of 35 patients with biochemical proof of disease and negative conventional imaging, [¹⁸F]DOPA PET had high positive and negative predictive value of 92% and 95% respectively. Thus, our findings support the use of [¹⁸F]DOPA PET scanning in the clinical workup of NET both in primary diagnosis and in staging and restaging of disease.

The localization of small primary of NETs is a challenge for diagnostic imaging. Furthermore, it is a

Figure 3 Fifty-seven-year-old female with abdominal pain imaged by CT, which revealed a 2 cm tumor in front of the inferior vena cava (arrow). (a) Fine needle biopsy of tumor indicated metastasis of NET, and therefore the patient was referred to [18F]DOPA PET-CT. In PET-CT, increased uptake of [18F]DOPA was detected in ileum (arrows) in addition to lymph node. (b–c) In operation, 2.7 cm primary tumor was resected from ileum (arrow) with a finding of lymph node. (d) Histological analysis confirmed NET with a proliferation index (Ki-67) of 5% and a metastatic lymph node.

well-established fact that surgery is the only curative approach in both local and advanced NETs. Even in the case of metastasized disease, it has been shown that the cytoreductive resection of the tumor mass appears to be beneficial and may result in improved long-term recovery in a significant number of patients (Wright *et al.* 2007). Furthermore, the extent of tumor spread determines the type of oncological treatment. Thus, an accurate diagnostic tool is of crucial importance for both diagnostic purposes and in planning treatment of NETs.

Anatomical imaging (CT and MRI) (Maurea *et al.* 1993, Pacak *et al.* 2001) and functional imaging (SRS and MIBG scintigraphy) (Krenning *et al.* 1993) had limited sensitivity in the diagnosis of NET. Nowadays, SRS and MIBG scintigraphy are routine in patients with suspicion of a NET and its sensitivity exceeds that of CT and MRI (Krenning *et al.* 1993, van der Harst *et al.* 2001). SRS is based on the expression of somatostatin receptors in endocrine tumors and, therefore, the density of these receptors determines the efficacy of this imaging method. Besides the staging of disease, SRS is used to assess the efficacy of treatment with somatostatin analogue. However, SRS has low sensitivity in localizing small tumors lacking somatostatin receptor 2, which is the case in 20–50% of NETs (Reubi *et al.* 1994). Furthermore, the labeled catecholamine analogue MIBG is another well-established tracer for scintigraphy visualization. However,

according to a recent review, up to 30% of carcinoid tumors had no accumulation of MIBG (Rufini *et al.* 2006), and scintigraphy seems to have limited sensitivity for the diagnosis of metastasized disease due to decreased expression of norepinephrine transporters by less differentiated cells. The sensitivity of MIBG scintigraphy was 57% in metastatic pheochromocytoma, and 92–96% in non-metastatic disease based on a series of 75 patients (van der Harst *et al.* 2001).

Initially, [^{18}F]FDG was used as a tracer in PET imaging in the diagnosis of NETs. Accumulation of [^{18}F]FDG in tumors is an index of increased glucose uptake, which reflects tumor aggressiveness, and, therefore, [^{18}F]FDG PET is more sensitive in localizing metastatic NETs (Adams *et al.* 1998, Timmers *et al.* 2007b). In ectopic ACTH-secreting NETs, Pacak and co-workers, in a series of 17 patients, reported no advance in localizing tumors using [^{18}F]FDG PET compared with conventional imaging (Pacak *et al.* 2004), whereas later on, one study reported successful localization of the disease in all three study patients (Kumar *et al.* 2006). Moreover, in localizing pheochromocytomas by [^{18}F]FDG PET, the sensitivity was 70% for solitary benign or malignant disease (Shulkin *et al.* 1999). The lack of sensitivity of [^{18}F]FDG PET in non-metastasized NET led to the studies of specifically targeted tracers that take advantage of the NET-specific catecholamine pathway. Based on the amine precursor uptake and

decarboxylation systems of the NET, the amine precursor, L-DOPA, was introduced as a specific tracer to image these tumors (Ahlstrom *et al.* 1995).

The mechanism that determines the uptake of [¹⁸F]DOPA PET in neuroendocrine tissues is not fully understood. Increased activity of L-DOPA decarboxylase was found to be characteristic of NETs (Gazdar *et al.* 1988), probably contributing to tracer uptake (Gibril & Jensen 2004). The radiolabeled L-DOPA is transported across the membrane by an amino acid transporter, after which it is decarboxylated in [¹⁸F]fluoro-dopamine and stored in vesicles. Although [¹⁸F]DOPA PET was first synthesized several years ago, only a few studies of [¹⁸F]DOPA PET have been published so far. This might be due to the difficult labeling procedure.

Our results, especially the high sensitivity of 100% for 25 patients with suspected pheochromocytoma, are in concordance with the previous findings. Previously, only one small study using [¹⁸F]DOPA PET for the primary diagnosis of NET in 14 patients with pheochromocytoma with a sensitivity up to 100% has been published (Pacak *et al.* 2001, Hoegerle *et al.* 2002). Furthermore, Hoegerle and co-workers studied 17 patients with carcinoid tumors with a sensitivity of 65% for [¹⁸F]DOPA PET imaging compared with anatomical imaging with sensitivity of 73%. Although the anatomical imaging modalities were more sensitive in organ metastases, [¹⁸F]DOPA PET was better in the localization of primary tumors and lymph node metastases (Hoegerle *et al.* 2001b). Subsequently, other studies of advanced-stage carcinoids showed [¹⁸F]DOPA PET to be more sensitive than conventional imaging in detecting skeletal lesions (Becherer *et al.* 2004), and it also found more tumor lesions per region compared with combined SRS and CT (96 vs 65%; Koopmans *et al.* 2006). Our finding is in agreement with these previous studies, since we found that [¹⁸F]DOPA PET detected significantly more tumor lesions than combined CT/MRI imaging ($P < 0.0001$). Recently, Montravers and co-workers concluded, in their study of 33 patients, that [¹⁸F]DOPA PET seems to be significantly more accurate in well-differentiated than in poorly differentiated NETs with an accuracy of 89% and 36% respectively (Montravers *et al.* 2006). Our results support this finding; when we analyzed the subgroup of patients with false-negative findings in [¹⁸F]DOPA PET imaging, five out of six patients had advanced neuroendocrine carcinoma.

There are also a few NET studies performed with other PET tracers. First, [¹¹C]5-HTP, another amino acid precursor, has been successfully used in the diagnosis of NETs. The study by Orlefors reported

that [¹¹C]5-HTP PET could detect more tumor lesions than SRS and CT in 58% of the study patients (Orlefors *et al.* 2005). Moreover, a recent preliminary study showed that somatostatin analogue, [⁶⁸Ga]DOTA-Tyr³-octreotide, is a promising new PET tracer in the diagnosis of NETs with a sensitivity of 97% and a specificity of 92% (Gabriel *et al.* 2007).

The main limitation of the present study was the lack of a pathological reference standard, although obtaining a biopsy specimen for histological verification from all participants with negative tests and several lesions is not feasible. Thus, we collected information during follow-up to confirm the true-positive and -negative findings. Another limitation is that conventional imaging studies, especially SRS and MIBG, were not performed systematically in all patients. The low accuracy of locating pancreatic NETs using [¹⁸F]DOPA PET is explained by the fact that the findings in ten patients with operatively treated insulinoma and β -cell hyperplasia have been published before with good results, and therefore were excluded from this report (Kauhanen *et al.* 2007). Furthermore, one argument concerning the use of [¹⁸F]DOPA in diagnosis suggests that non-functioning tumors may be difficult to detect, since accumulation reflects the secretion pattern of peptide hormones. However, the hypothesis that only amine-producing tumors can be imaged by [¹⁸F]DOPA PET has to be proved in further studies. According to our findings, even silent tumors without biochemical findings of a NET could be detected by [¹⁸F]DOPA PET.

Recently, several groups have suggested that inhibiting the peripheral decarboxylation can enhance tumor accumulation of HTP and DOPA. The decarboxylase inhibitor carbidopa, given as per oral premedication decreases the renal excretion and, at the same time, increases tumor uptake, hence improving visualization of the tumor (Eriksson *et al.* 2000, Orlefors *et al.* 2006, Timmers *et al.* 2007a). The physiological rather high uptake of the pancreas also disappears. In our institution, we have started to use premedication since May 2006 among NET patients except for pancreatic tumors. In this study, only 19 patients had premedication with carbidopa. The finding of increased sensitivity of [¹⁸F]DOPA PET after carbidopa is important and should be studied further with NETs of various organs. However, its routine use is not recommended with pancreatic tumors (except carcinoids) since pancreatic physiological uptake disappears, and it has not been confirmed that tumor uptake would not also disappear along with this (Kauhanen *et al.* 2008). Moreover, a further development has been combined PET-CT, which provides

improved anatomical localization. In our study, 70 patients had combined PET-CT, although no statistical difference was observed between the accuracy of PET and PET-CT ($P=0.24$).

We have used [^{18}F]DOPA for almost a decade as a tracer in PET imaging of NETs. Our experiences are in accordance with the previous studies. However, all larger previous studies (Becherer *et al.* 2004, Hoegerle *et al.* 2001b, Koopmans *et al.* 2006, Montravers *et al.* 2006) included mostly patients with advanced NETs. To our knowledge, present study is the first to assess [^{18}F]DOPA PET in the primary diagnosis of NETs in various organs and our study is the largest reporting accurate diagnosis of pheochromocytoma using [^{18}F]DOPA PET, as well.

The main goal of the study was to analyze the clinical value of [^{18}F]DOPA PET in patients with suspicion of primary NET and positive biochemistry or restaging of disease. We conclude that in patients with a suspected NET but negative or inconclusive conventional imaging findings, [^{18}F]DOPA PET gives extremely useful information. This is especially true whenever pheochromocytoma is suspected. Furthermore, in patients with a formerly known NET and increasing tumor markers, [^{18}F]DOPA PET is a highly sensitive first-line imaging method in detecting a recurrent NET. Combined [^{18}F]DOPA PET-CT could be a one-step procedure not only in the staging of a NET but also in the primary diagnosis and follow-up.

Declaration of interest

The authors have nothing to disclose.

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References

Adams S, Baum R, Rink T, Schumm-Drager PM, Usadel KH & Hor G 1998 Limited value of fluorine-18

fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. *European Journal of Nuclear Medicine* **25** 79–83.

Ahlstrom H, Eriksson B, Bergstrom M, Bjurling P, Langstrom B & Oberg K 1995 Pancreatic neuroendocrine tumors: diagnosis with PET. *Radiology* **195** 333–337.

Becherer A, Szabo M, Karanikas G, Wunderbaldinger P, Angelberger P, Raderer M, Kurtaran A, Dudczak R & Kletter K 2004 Imaging of advanced neuroendocrine tumors with (18)F-FDOPA PET. *Journal of Nuclear Medicine* **45** 1161–1167.

Bergman J, Haaparanta M, Lehtikainen P & Solin O 1994 Electrophilic synthesis of 6-18Ffluoro-L-dopa starting from aqueous-18Ffluoride. *Journal of Labelled Compounds & Radiopharmaceuticals* **35** 476–477.

Eriksson B, Bergstrom M, Orlefors H, Sundin A, Oberg K & Langstrom B 2000 Use of PET in neuroendocrine tumors. *In vivo applications and in vitro studies. Quarterly Journal of Nuclear Medicine* **44** 68–76.

Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R & Virgolini IJ 2007 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *Journal of Nuclear Medicine* **48** 508–518.

Gazdar AF, Helman LJ, Israel MA, Russell EK, Linnoila RI, Mulshine JL, Schuller HM & Park JG 1988 Expression of neuroendocrine cell markers L-dopa decarboxylase, chromogranin A, and dense core granules in human tumors of endocrine and nonendocrine origin. *Cancer Research* **48** 4078–4082.

Gibril F & Jensen RT 2004 Diagnostic uses of radiolabelled somatostatin receptor analogues in gastroenteropancreatic endocrine tumours. *Digestive and Liver Disease* **36** S106–S120.

van der Harst E, de Herder WW, Bruining HA, Bonjer HJ, de Krijger RR, Lamberts SW, van de Meiracker AH, Boomsma F, Stijnen T, Krenning EP *et al.* 2001 [(123)I]metaiodobenzylguanidine and [(111)In]octreotide uptake in benign and malignant pheochromocytomas. *Journal of Clinical Endocrinology and Metabolism* **86** 685–693.

Hoegerle S, Althoefer C, Ghanem N, Brink I, Moser E & Nitzsche E 2001a 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. *European Journal of Nuclear Medicine* **28** 64–71.

Hoegerle S, Althoefer C, Ghanem N, Koehler G, Waller CF, Scheruebl H, Moser E & Nitzsche E 2001b Whole-body 18F dopa PET for detection of gastrointestinal carcinoid tumors. *Radiology* **220** 373–380.

Hoegerle S, Nitzsche E, Althoefer C, Ghanem N, Manz T, Brink I, Reincke M, Moser E & Neumann HP 2002 Pheochromocytomas: detection with 18F DOPA whole body PET – initial results. *Radiology* **222** 507–512.

- Hoegerle S, Ghanem N, Althoefer C, Schipper J, Brink I, Moser E & Neumann HP 2003 18F-DOPA positron emission tomography for the detection of glomus tumours. *European Journal of Nuclear Medicine and Molecular Imaging* **30** 689–694.
- Jadvar H & Segall GM 1997 False-negative fluorine-18-FDG PET in metastatic carcinoid. *Journal of Nuclear Medicine* **38** 1382–1383.
- Kauhanen S, Seppanen M, Minn H, Gullichsen R, Salonen A, Alanen K, Parkkola R, Solin O, Bergman J, Sane T *et al.* 2007 Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography as a tool to localize an insulinoma or β -cell hyperplasia in adult patients. *Journal of Clinical Endocrinology and Metabolism* **92** 1237–1244.
- Kauhanen S, Seppanen M & Nuutila P 2008 Premedication with carbidopa masks positive finding of insulinoma and beta-cell hyperplasia in [^{18}F]-dihydroxy-phenyl-alanine positron emission tomography. *Journal of Clinical Oncology* **26** 5307–5308.
- Kloppel G, Rindi G, Anlauf M, Perren A & Komminoth P 2007 Site-specific biology and pathology of gastroenteropancreatic neuroendocrine tumors. *Virchows Archiv* **451** S9–S27.
- Koopmans KP, de Vries EG, Kema IP, Elsinga PH, Neels OC, Sluiter WJ, van der Horst-Schrivers AN & Jager PL 2006 Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncology* **7** 728–734.
- Koopmans KP, Neels OC, Kema IP, Elsinga PH, Sluiter WJ, Vanghillewe K, Brouwers AH, Jager PL & de Vries EG 2008 Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. *Journal of Clinical Oncology* **26** 1489–1495.
- Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, van Hagen M, Postema PT, de Jong M & Reubi JC 1993 Somatostatin receptor scintigraphy with [^{111}In -DTPA-D-Phe 1]- and [^{123}I -Tyr 3]-octreotide: the Rotterdam experience with more than 1000 patients. *European Journal of Nuclear Medicine* **20** 716–731.
- Kumar J, Spring M, Carroll PV, Barrington SF & Powrie JK 2006 18Fluorodeoxyglucose positron emission tomography in the localization of ectopic ACTH-secreting neuroendocrine tumours. *Clinical Endocrinology* **64** 371–374.
- Maurea S, Cuocolo A, Reynolds JC, Tumeh SS, Begley MG, Linehan WM, Norton JA, Walther MM, Keiser HR & Neumann RD 1993 Iodine-131-metaiodobenzylguanidine scintigraphy in preoperative and postoperative evaluation of paragangliomas: comparison with CT and MRI. *Journal of Nuclear Medicine* **34** 173–179.
- Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle FG, Kaltsas GA, Krenning EP *et al.* 2008 Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncology* **9** 61–72.
- Montravers F, Grahek D, Kerrou K, Ruszniewski P, de B V, Aide N, Gutman F, Grange JD, Lotz JP & Talbot JN 2006 Can fluorodihydroxyphenylalanine PET replace somatostatin receptor scintigraphy in patients with digestive endocrine tumors? *Journal of Nuclear Medicine* **47** 1455–1462.
- Orlefors H, Sundin A, Garske U, Juhlin C, Oberg K, Skogseid B, Langstrom B, Bergstrom M & Eriksson B 2005 Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. *Journal of Clinical Endocrinology and Metabolism* **90** 3392–3400.
- Orlefors H, Sundin A, Lu L, Oberg K, Langstrom B, Eriksson B & Bergstrom M 2006 Carbidopa pretreatment improves image interpretation and visualisation of carcinoid tumours with 11C-5-hydroxytryptophan positron emission tomography. *European Journal of Nuclear Medicine and Molecular Imaging* **33** 60–65.
- Otonkoski T, Nanto-Salonen K, Seppanen M, Veijola R, Huopio H, Hussain K, Tapanainen P, Eskola O, Parkkola R, Ekstrom K *et al.* 2006 Noninvasive diagnosis of focal hyperinsulinism of infancy with [^{18}F]-DOPA positron emission tomography. *Diabetes* **55** 13–18.
- Pacak K, Eisenhofer G, Carrasquillo JA, Chen CC, Li ST & Goldstein DS 2001 6-[^{18}F]fluorodopamine positron emission tomographic (PET) scanning for diagnostic localization of pheochromocytoma. *Hypertension* **38** 6–8.
- Pacak K, Ilias I, Chen CC, Carrasquillo JA, Whatley M & Nieman LK 2004 The role of [^{18}F]fluorodeoxyglucose positron emission tomography and [^{111}In]-diethylenetriaminepentaacetate-D-Phe-pentetreotide scintigraphy in the localization of ectopic adrenocorticotropin-secreting tumors causing Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* **89** 2214–2221.
- Pasquali C, Rubello D, Sperti C, Gasparoni P, Liessi G, Chierichetti F, Ferlin G & Pedrazzoli S 1998 Neuroendocrine tumor imaging: can 18F-fluorodeoxyglucose positron emission tomography detect tumors with poor prognosis and aggressive behavior? *World Journal of Surgery* **22** 588–592.
- Pearse AG 1969 The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. *Journal of Histochemistry and Cytochemistry* **17** 303–313.
- Reubi JC, Schaer JC, Waser B & Mengod G 1994 Expression and localization of somatostatin receptor SSTR1, SSTR2, and SSTR3 messenger RNAs in primary human tumors using *in situ* hybridization. *Cancer Research* **54** 3455–3459.
- Rufini V, Calcagni ML & Baum RP 2006 Imaging of neuroendocrine tumors. *Seminars in Nuclear Medicine* **36** 228–247.

- Shulkin BL, Thompson NW, Shapiro B, Francis IR & Sisson JC 1999 Pheochromocytomas: imaging with 2-[fluorine-18]fluoro-2-deoxy-D-glucose PET. *Radiology* **212** 35–41.
- Timmers HJ, Hadi M, Carrasquillo JA, Chen CC, Martiniova L, Whatley M, Ling A, Eisenhofer G, Adams KT & Pacak K 2007a The effects of carbidopa on uptake of 6-18F-Fluoro-L-DOPA in PET of pheochromocytoma and extraadrenal abdominal paraganglioma. *Journal of Nuclear Medicine* **48** 1599–1606.
- Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, Adams KT, Solis D, Lenders JW & Pacak K 2007b Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. *Journal of Clinical Oncology* **25** 2262–2269.
- Trampal C, Engler H, Juhlin C, Bergstrom M & Langstrom B 2004 Pheochromocytomas: detection with 11C hydroxyephedrine PET. *Radiology* **230** 423–428.
- Wright BE, Lee CC & Bilchik AJ 2007 Hepatic cytoreductive surgery for neuroendocrine cancer. *Surgical Oncology Clinics of North America* **16** 627–637.