^{18}F-Fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type

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Abstract 6-Fluoro-(^{18}F)-L-3,4-dihydroxyphenylalanine (FDOPA) is an amino acid analogue for positron emission tomography (PET) imaging which has been registered since 2006 in several European Union (EU) countries and by several pharmaceutical firms. Neuroendocrine tumour (NET) imaging is part of its registered indications. NET functional imaging is a very competitive niche, competitors of FDOPA being two well-established radiopharmaceuticals for scintigraphy, ^{123}I-metaiodobenzylguanidine (MIBG) and ^{111}In-pentetreotide, and even more radiopharmaceuticals for PET, including fluorodeoxyglucose (FDG) and somatostatin analogues. Nevertheless, there is no universal single photon emission computed tomography (SPECT) or PET tracer for NET imaging, at least for the moment. FDOPA, as the other PET tracers, is superior in diagnostic performance in a limited number of precise NET types which are currently medullary thyroid cancer, catecholamine-producing tumours with a low aggressiveness and well-differentiated carcinoid tumours of the midgut, and in cases of congenital hyperinsulinism. This article reports on diagnostic performance and impact on management of FDOPA according to the NET type, emphasising the results of comparative studies with other radiopharmaceuticals. By pooling the results of the published studies with a defined standard of truth, patient-based sensitivity to detect recurrent medullary thyroid cancer was 70 % [95 % confidence interval (CI) 62.1–77.6] for FDOPA vs 44 % (95 % CI 35–53.4) for FDG; patient-based sensitivity to detect phaeochromocytoma/paraganglioma was 94 % (95 % CI 91.4–97.1) for FDOPA vs 69 % (95 % CI 60.2–77.1) for ^{123}I-MIBG; and patient-based sensitivity to detect midgut NET was 89 % (95 % CI 80.3–95.3) for FDOPA vs 80 % (95 % CI 69.2–88.4) for somatostatin receptor scintigraphy with a larger gap in lesion-based sensitivity (97 vs 49 %). Previously unpublished FDOPA results from our team are reported in some rare NET, such as small cell prostate cancer, or in emerging indications, such as metastatic NET of unknown primary (CUP-NET) or adrenocorticotropic hormone (ACTH) ectopic production. An evidence-based strategy in NET functional imaging is as yet affected by a low number of comparative studies. Then the suggested diagnostic trees, being a consequence of the analysis of present data, could be modified, for some indications, by a wider experience mainly involving face-to-face studies comparing FDOPA and ^{68}Ga-labelled peptides.

Keywords Neuroendocrine tumour · PET/CT · ^{18}F-FDOPA · ^{18}F-FDG · ^{68}Ga-DOTATOC · Somatostatin receptor scintigraphy · MIBG

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Neuroendocrine tumours (NET) are derived from endocrine cells; they usually contain secretory granules and have the capacity to produce biogenic amines and polypeptide hormones. These tumours often pose a difficult diagnostic

challenge because of their small size and multiplicity. Nevertheless, an accurate staging of NET is important for the determination of resectability and of the prognosis. In 156 NET patients with the gastroenteropancreatic (GEP) type, the 5-year survival rate was lower (50 %) in 20 patients with extrahepatic secondary lesions than in 61 patients with only hepatic metastases (73 %) or 18 patients with nodal involvement (77 %) or in those with only local disease (96 %) [1]. The presence of extrahepatic sites of disease, bone metastases in particular, has been suggested to be a marker of a subgroup of patients with a worse prognosis and shorter survival [2] who would benefit more from aggressive therapeutic approaches.

Somatostatin receptor scintigraphy (SRS) with single photon emission computed tomography (SPECT), using ^{111}In-pentetreotide or another somatostatin analogue labelled with ^{99m}Tc, detects the presence of somatostatin receptors, mainly the subtype 2. SRS is still currently the reference nuclear medicine investigation in NET. Being a whole-body examination, it is convenient for staging, with drawbacks linked to its biodistribution: a high activity in the liver, the spleen and delayed gut activity due to biliary excretion. SRS also has a clear limitation due to its poor spatial resolution to characterise suspicious lesions smaller than 10 mm on anatomic imaging modalities or to discover unsuspected small-sized lesions. Another cause of false-negative results is a lack of somatostatin receptor subtype 2 on the tumour tissue. In contrast, it has the advantage, when positive, to predict response to somatostatin analogue treatment [3].

An alternative to SRS is metaiodobenzylguanidine (MIBG) scintigraphy and SPECT, which is almost exclusively used in NET for imaging phaeochromocytomas, chemodectomas and rarely some NET of the ileum or medullary thyroid cancer (MTC). [123]I or ^{131}I have been both used for MIBG scintigraphy, but ^{123}I-MIBG yields images with better resolution and a better signal for SPECT(/CT) and is currently the most widely reported for diagnostic application.

To take advantage of the superior resolution and the accurate uptake quantification offered by positron emission tomography (PET), several tracers have been proposed for a more effective functional imaging of NET. Currently, the only one that obtained a marketing authorisation (MA) in the European Union (EU) explicitly mentioning NET is 6-fluoro-(^{18}F)-L-3,4-dihydroxy-phenylalanine (FDOPA). Other "specific" NET tracers such as 6-fluoro-([18])-fluorodopamine (FDA) or the serotonin precursor 5-hydroxytryptophan (5-HTP) labelled with ^{11}C have been proposed as well as several somatostatin analogues labelled with positron-emitting radionuclides, ^{68}Ga in most cases (SRPET or SRPET/CT on hybrid PET/CT machines).

Importantly, poorly differentiated neuroendocrine cancers with little or no hormone production and a high proliferative activity usually take up ^{18}F-fluorodeoxyglucose (FDG) as do most "common" cancers [4, 5], while sensitivity of NET tracers is poor.

FDOPA vs other radiopharmaceuticals

FDOPA has been used for PET imaging in humans for more than two decades, initially for studying the physiology and physiopathology of dihydroxyphenylalanine (DOPA) biodistribution in the human brain, in particular Parkinson's syndrome, and then in oncology for NET or brain tumours. The pathophysiological rationale for PET imaging of NET with FDOPA is that several types of NET tumours are able to take up, decarboxylate and store amino acids, such as DOPA, and their biogenic amines [6, 7]. MA was granted for a commercial preparation of FDOPA in France in 2006, and others since then; and this radiopharmaceutical is commercially available.

Of the radiopharmaceuticals which are authorised by the French medicines agency for use in this context in our department, the least expensive is ^{18}F-FDG, followed by ^{123}I-MIBG, then ^{68}Ga-edotreotide (^{68}Ga-DOTATOC) and ^{111}In-pentetreotide, ^{18}F-FDOPA being the most expensive. This is due to a complicated process of ^{18}F-FDOPA labelling which requires [18]F$_2$ gas instead of ^{18}F-fluoride ion and has a low yield. However, the cost of the whole imaging examination integrates many other factors such as the time spent by the radiopharmacist and the technologist for the on-site preparation of the injection, the longest for DOTATOC, and the duration of the image acquisition, far longer with SPECT than with PET, impacting on the cost of the personnel and the workflow of the machine. The cost of the multiple transportations of the patient for the multiple scans which are recommended with MIBG or SRS should be taken into account. All those factors clearly reduce the gap in cost between FDOPA PET/CT, a rapid procedure, and SPECT/CT.

Furthermore, in the benefit-cost ratio, the benefit is not equal for all those radiopharmaceuticals. As will be further discussed in this article, the diagnostic performance of all those radiopharmaceuticals differs according to the type of the NET. A patient-based analysis of diagnostic performance is important, in particular for the detection of residual tumour after a radical treatment, but a lesion- or site-based analysis is also important as evaluating the real extension of the disease is a key element for tumour resectability and surgical procedure with curative intent. The benefit, evaluated by the impact on patient management, also depends on the potential use of internal radiotherapy revealed by the imaging modality. MIBG uptake by NET tumours may pave the way to ^{131}I-MIBG internal radiotherapy which had been granted MA for

several years to target NETs as well as neuroblastoma, and similarly a positive somatostatin analogue imaging opens the option of internal radiotherapy with ^{90}Y- or ^{177}Lu-labelled ligands of somatostatin receptors [8]. There is no such direct link with FDOPA or FDG imaging. But actually a radiopharmaceutical with a different functional approach is an advantage for indicating and monitoring internal radiotherapy: by comparing images of FDOPA PET/CT and MIBG SPECT or SRPET, tumours only taking up FDOPA can be delineated which are less likely to respond to the planned radiotherapy or have resisted to a past attempt, while the receptor-bearing tumours could have responded, leading to false-negative results when monitoring with the corresponding radiopharmaceutical.

FDOPA PET and PET/CT

The practice for FDOPA PET imaging in NET is not fully standardised at the moment. A 4-h fast is recommended by all teams, but sugar intake may be authorised in particular in hypoglycaemic patients. The oral premedication with the decarboxylase inhibitor carbidopa, which was introduced to block the aromatic amino acid decarboxylase enzyme, is less common than for brain FDOPA imaging. Eriksson et al. [9] reported that this administration led to a sixfold decrease in renal excretion while the tumour uptake increased threefold. Concordantly, Timmers et al. [10] reported that, compared with baseline FDOPA PET, carbidopa pretreatment resulted in the detection of 3 additional lesions in 3 of 11 patients with phaeochromocytoma or extra-adrenal paraganglioma. In contrast, in one infant in the series of Ribeiro et al. [11] the diffuse uptake of FDOPA in the pancreas completely disappeared under carbidopa treatment, while the kidney activity was still present: the patient had histologically proven diffuse abnormal pancreatic cells scattered in the whole pancreas. Similar findings were reported by Kauhanen et al. in 2008 in two of three adults with insulinoma. These findings do not favour the use of carbidopa in patients with pancreatic tumours since pancreatic physiological uptake disappears, and tumour uptake could not also disappear along with this [12].

The range of injected activity is 2–4 MBq/kg of body mass according to the MA, typically 150–400 MBq, reflecting the rapid evolution of PET machines, from 2-D acquisition to 3-D and then time-of-flight acquisition, allowing a reduction in injected activity. According to International Commission on Radiological Protection (ICRP) 106 (2008 vol. 38), the effective dose after IV injection of ^{18}-FDOPA is 0.025 mSv/MBq in adults and 0.10 mSv/MBq in a 1-year-old child.

The FDOPA uptake by most organs and target lesions has been described as a plateau between 30 and 90 min post-injection [10]; there was no advantage of the 90-min scan over the 30-min scan, visually or with determination of standardized uptake value (SUV), in a series of 23 patients with various NET [13]. Thus, the starting time of whole-body image acquisition usually ranges between 45 and 65 min post-injection. However, early image acquisition 15–20 min after injection is useful in some indications, in particular MTC [14] or phaeochromocytoma [15].

In cases of metastatic NET, FDOPA is taken up not only by the soft tissue lesions but also by the bone metastases. In a series of 23 patients with advanced stage NET, FDOPA accurately detected skeletal lesions (sensitivity of 100 % and specificity of 91 %), even in 40 % of patients with a negative CT scan [13].

FDOPA PET is now performed on hybrid machines which provide PET/CT fusion and increase diagnostic performance. In a study comparing FDOPA PET/CT, PET or CT alone in MTC [16], PET identified all 18 lesions as positive, but was unable to definitively localise 4 lesions (22 %); CT could localise all 18 lesions, but could not definitively diagnose or exclude MTC in 6 lesions (33 %); only FDOPA PET/CT accurately characterised and localised all 18 lesions. Similar results demonstrating the superiority of FDOPA PET/CT over FDOPA PET and CT alone have been reported in phaeochromocytoma [17], midgut carcinoid tumours or pancreatic islet cell tumours [18].

False-positive results in inflammatory lesions that are frequent with FDG PET seem to be very rare with FDOPA PET. There is in fact one single report in oncology published as an abstract [19]: on FDOPA PET performed during treatment evaluation of a small cell neuroendocrine laryngeal carcinoma, a mediastinal hot spot corresponded to sarcoidosis. Nevertheless, the possibility of an inflammatory lesion should be kept in mind when an unexpected FDOPA focus is detected. The physiological diffuse uptake in the pancreas, and in the gallbladder leading to gut activity, may cause some problems in the interpretation.

As our team previously demonstrated by comparing the uptake of several tracers, NET does not constitute a biologically and metabolically homogeneous group of tumours [20, 21]. We will thus report on the utility of FDOPA by distinguishing the major types of NET and emphasising recent comparative studies with other radiopharmaceuticals. An evidence-based strategy in NET functional imaging is as yet affected by a low number of comparative studies. Then the suggested diagnostic trees, being a consequence of the analysis of present data, could be modified, for some indications, by a wider experience mainly involving face-to-face studies comparing FDOPA and ^{68}-labelled peptides.

Medullary thyroid cancer

The initial study by Hoegerle et al. [22] compared, in 11 MTC patients, FDOPA PET with the established functional and morphological imaging methods, including FDG PET. A recent meta-analysis of eight studies on suspected recurrent MTC found the patient-based detection rate for FDOPA PET(/CT) to be 66 and 71 % for lesion-based analysis, which is an operational result in cases of occult recurrent disease [23]. All published studies have confirmed the superiority of FDOPA over all other radiopharmaceuticals [16, 22, 24–32] (Table 1), in particular in the detection of metastatic lymph nodes [22, 32] (Fig. 1). When compared to morphological imaging, FDOPA has a clear advantage for specificity [22, 29]. Pooling the results of three studies [26, 32, 33], the impact of FDOPA PET(/CT) estimated by the rate of changes in patient management is 20/59 =34 %. The performance of FDOPA varies according to the serum levels of the two biochemical markers, calcitonin (CTN) and carcinoembryonic antigen (CEA).

In the comparative study by Koopmans et al. [27], FDOPA was the most sensitive imaging modality, but of eight patients with CTN <500 ng/l FDOPA was positive in only one (CTN=86 ng/l, CEA=1.1 μg/l) and FDG in another one (CTN =73 ng/l, CEA =1.2 μg/l). In the study of Luster et al. [16], no true-positive FDOPA PET/CT case was found in patients with basal CTN <60 ng/l, and conversely, no true-negative PET/CT case was found in patients with basal CTN >120 ng/l. FDOPA PET/CT had 100 % sensitivity and specificity when CTN at the time of scanning was >150 ng/l.

FDG may detect lesions missed by FDOPA. In the series of Marzola et al., FDOPA was positive alone in 5/18 patients, but FDG was positive alone in 1 patient and showed more lesions in 2 others [28]. In the series of Kauhanen et al., for a CEA doubling time of less than 24 months, FDG PET/CT correctly detected metastases in 80 % of patients and FDOPA PET/CT in 60 % [29]. An efficacy of FDG in cases of short doubling time of serum CTN and CEA levels has been confirmed by Verbeek et al. [30], FDG PET positivity being an indicator for poor survival, while FDOPA PET detected significantly more lesions (56/75=75 %) than did FDG PET (35/75=47 %) in 21 patients. This relation between FDG uptake, short CTN doubling time and progression of metastatic MTC had already been noted: of 11 patients with positive FDG PET, 6 died from metastatic disease and 4 had disease progression; of 12 patients with negative FDG PET, 1 had recurrent disease, and 11 had no evidence of clinical disease [31].

In 10 of the 18 patients of the Italian co-operative comparative study, FDOPA PET/CT identified significantly more lesions than FDG PET/CT and SRPET/CT, whereas in one patient FDG PET/CT revealed multiple liver lesions missed by both FDOPA PET/CT and SRPET/CT as well as two additional locoregional lymph nodes [32]. No additional lesions were identified by SRPET/CT.

The results of another study comparing FDG and SRPET in 18 patients with recurrent MTC are concordant: SRPET/CT achieved disease detection in 13 of 18 patients (72 %) and FDG PET/CT in 14 of 18 (78 %) patients; FDG revealed a total of 28 metastatic MTC regions and SRPET 23 regions [34]. Of eight patients with occult biochemical recurrence of MTC, FDG negative and FDOPA not performed, reported by Pałyga et al., SRPET/CT localised in two cases the recurrent cervical lymph nodes which were confirmed after resection [35]. The same proportion (one of four) was observed by another Polish team [36].

FDG showed a superior diagnostic performance when compared to all SPECT radiopharmaceuticals: ^{123}I-MIBG [37, 38], pentavalent ^{99m}Tc-dimercaptosuccinic acid [4, 37, 39], ^{99m}Tc-sestamibi [37] or somatostatin analogues for SRS [37, 39–41], with the exception of the earliest study [22]. SRS appeared to be less sensitive than conventional imaging at detecting the full extent of metastatic disease in 11 children and adolescents with hereditary MTC [42].

In conclusion, data have been obtained mostly in cases of rising tumour marker levels after thyroidectomy. In this context, imaging is recommended if CTN is >150 ng/ml [43]. FDOPA is the best tracer; an early image acquisition starting during the first 15 min is advised [14] (Fig. 1). In negative cases, FDG should be the next PET tracer, in particular if CEA levels are elevated or rapidly rising [27, 29–32], and SRPET when neither FDOPA nor FDG PET are contributive [34–36].

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare and aggressive NET derived from cells located in the basal layers of the epidermis. Its clinical behaviour is characterised by aggressive regional nodal invasion, distant metastases and a high rate of recurrence, appearing in the majority of cases within the first 6–12 months after initial diagnosis.

Whole-body imaging is useful to stage and restage the tumour as well as sentinel lymph node detection for resection. The functional imaging modalities proposed for the detection of distant lesions of MCC were, like in most NET, ^{131}I-MIBG SPECT [44], SRS [45] and FDG PET [46].

MCC shares similarities with both cutaneous melanoma and small cell carcinoma of the lung, which both evidenced uptake of FDOPA. Our team [47] observed that FDOPA was taken up in two MCC cases and true-negative in one suspected recurrence on SRS. However, the contrast of the images was lower with FDOPA than with FDG. The team in Vienna obtained similar results on 5 FDOPA PETs vs 24

Table 1 FDOPA and comparators in MTC: comparative studies with a standard of truth

Reference	No. of patients	FDOPA imaging technique	Performances of FDOPA imaging	Performances of comparator
Hoegerle et al. (2001) [22]	11 patients with elevated calcitonin levels	PET	Se lesion based	
			Overall	
	27 lesions		17/27=63 %	FDG 12/27=44 %
				SRS 14/27=52 %
				CT or MRI 22/27=81 %
			Primary tumour/local recurrence	
			2/3=66 %	FDG 2/3=66 %
				SRS 2/3=66 %
				CT or MRI 3/3=100 %
			Lymph node metastases	
			14/16=88 %	FDG 7/16=44 %
				SRS 8/16=50 %
				CT or MRI 11/16=69 %
			Organ metastases	
			1/8=13 %	FDG 3/8=38 %
				SRS 4/8=50 %
				CT or MRI 8/8=100 %
			Sp lesion based	
			Overall	
			21/22=95 %	FDG 22/22=100 %
				SRS 22/22=100 %
				CT or MRI 18/27=67 %
			Primary tumour/local recurrence	
			8/8=100 %	FDG 8/8=100 %
				SRS 8/8=100 %
				CT or MRI 6/11=55 %
			Lymph node metastases	
			5/5=100 %	FDG 5/5=100 %
				SRS 5/5=100 %
				CT or MRI 4/7=57 %
			Organ metastases	
			8/9=89 %	FDG 9/9=100 %
				SRS 9/9=100 %
				CT or MRI 8/9=89 %
Beuthien-Baumann et al. (2007) [25]	15 patients with recurrent or metastatic MTC	PET	Patient-based detection rate	
	FDG 15 patients		8/15=53 %	FDG 7/15=47 %
	OMFD 10 patients			OMFD 1/10=10 %
Koopmans et al. (2008) [27]	21 patients with biochemical recurrence of MTC, 134 lesions	PET	Se patient based	
			13/21=62 %	FDG 4/17=24 %
	FDG 17 patients/102 lesions			DMSA-V 5/18=28 %
	DMSA-V 18 patients/108 lesions			MRI or CT 7/18=39 %
			Se lesion based	
	MRI or CT 18 patients/ 126 lesions		95/134=71 %	FDG 48/102=30 %
				DMSA-V 20/ 108=19 %

Table 1 (continued)

Reference	No. of patients	FDOPA imaging technique	Performances of FDOPA imaging	Performances of comparator
				MRI or CT 80/126=64 %
			For all imaging modalities Se 2/8=25 % if serum calcitonin baseline levels <500 ng/l	
Beheshti et al. (2009) [26]	26 patients with MTC and elevated calcitonin levels 53 lesions	PET/CT	Se patient based	
			21/26=81 %	FDG 15/26=58 %
			Detection rate for malignant lesions	
			50/53=94 %	FDG 33/53=62 %
				CT 34/53=64 %
Luster et al. (2010) [16]	Follow-up of MTC 28 examinations, 26 patients	PET and PET/CT	Se patient based	
			PET/CT 14/19=74 %	CT 13/19=68 %
			Sp patient based	
			PET/CT 9/9=100 %	CT 7/9=78 %
			In relation to serum calcitonin baseline levels	
			< 60 ng/l → 0 TP results	
			>120 ng/l → 0 TN results	
			>150 ng/l → Se & Sp=100 %	
Marzola et al. (2010) [28]	18 patients with occult recurrence of MTC	PET/CT	Patient-based detection rate	
			15/18=83 %	FDG 11/18=61 %
				CT 9/18=50 %
Kauhanen et al. (2011) [29]	19 patients with occult recurrence of MTC, 118 regions	PET/CT	Patient-based detection rate	
			11/19=58 %	FDG 10/19=53 %
				MDCT 9/19=47 %
				MRI 10/17=59 %
			Region-based detection rate	
			61/118=52 %	FDG 55/118=47 %
				MDCT 54/118=46 %
				MRI 92/118=78 %
Treglia et al. (2012) [32]	18 patients with occult recurrence of MTC, 72 lesions	PET/CT	Patient-based sensitivity	
			13/18=72 %	SRPET 6/18=33 %
				FDG 3/18=17 %
			Lesion-based sensitivity	
			61/72=85 %	SRPET 14/72=20 %
				FDG 20/72=28 %
Overall	156 patients		Se patient based	
			95/136=70 % (95 % CI 62.1–77.6)	FDG 50/113=44 % (95 % CI 35–53.4)
			Se lesion based	
			284/404=70 % (95 % CI 65.8–74.8)	FDG 156/372=42 % (95 % CI 36.9–46.9)

CI confidence interval, *DMSA-V* pentavalent dimercaptosuccinic acid scintigraphy and SPECT, *MTC* medullary thyroid cancer, *OMFD* 3-O-methyl-6-[^{18}F]fluoro-DOPA, *MD* multidetector, *Se* sensitivity,*Sp* specificity, *SRS* somatostatin receptor scintigraphy using ^{111}In-pentetreotide

FDG PETs [48]. In further series, the elective radiopharmaceutical was FDG, with a clear utility to detect nodal basin involvement (sensitivity=83 %, specificity=95 % for FDG vs 0 and 86 % for MRI, respectively) [49], as well as

distant metastases [50], performing better than SRS [51], but with some false-negative results [52] probably in less aggressive forms.

In conclusion, FDG should be the first-line functional examination in MCC. When negative, it could be completed with SRPET.

Small cell lung cancer

Being a whole-body technique, PET can play a major role for a rapid staging of small cell lung cancer (SCLC) needed by the urgent therapeutic decision: FDG PET has been proposed for this purpose [53]. Since SCLC shares metabolic characteristics with NET, we speculated that FDOPA could be useful, being more specific than FDG and able to detect brain metastases. FDOPA and FDG PET were performed in four patients with newly diagnosed SCLC [54]. FDOPA PET appeared less sensitive than FDG PET and standard imaging procedures in the staging of SCLC. The utility of FDG PET for SCLC imaging has been confirmed in larger series [55].

In conclusion, FDG and not FDOPA is the reference tracer in SCLC.

Bronchial carcinoids

Bronchial carcinoids (BC) are histologically classified into typical (ca. 90 %) or atypical, with consequences on management. To the best of our knowledge, only a few cases have been reported using FDOPA PET: one was positive only on early images [56], and, by pooling the results of two comparative studies [56, 57] in a total of 8 patients, the FDOPA patient-based detection rate was 4/8 =50 % vs 7/8 =88 % for SRPET which showed more foci than FDOPA in 2/4 cases.

SRPET/CT was performed in 11 patients to stage BC; the detection rate was 9/11 =82 %, leading to a change in management of 3 of these 9 patients [58]. FDG uptake by the primary BC lesion is also frequent: by pooling the results of 4 studies, it was 36/42 =86 % [59–62]. However, no metastatic BC was included in those series.

Very concordant results can be derived from two comparative studies of SRPET/CT and FDG PET/CT [63, 64], in a total of 24 typical and 9 atypical BC: typical BC showed higher and more selective uptake on SRPET/CT than on FDG PET/CT, while the reverse was observed for atypical BC and higher grades of lung NET. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia showed no uptake either on SRPET/CT or on FDG PET/CT. These results are in accordance with the classification of BC into the "foregut" group [65], with good overall results for SRS or SRPET in cases of well-differentiated NET.

In conclusion, if BC staging is found clinically useful, SRPET could be recommended, except in cases of atypical BC where FDG could be recommended as first line.

## Paraganglioma, phaeochromocytoma and glomus tumour

Paragangliomas (PG) derive from the sympathetic or the parasympathetic systems, which comprise phaeochromocytomas derived from chromaffin cells in the adrenal gland, extra-adrenal sympathetic PG and parasympathetic PG, in particular glomus tumours and chemodectomas. The current reference radiopharmaceutical for scintigraphy is MIBG that traces expression of tumour-specific catecholamine transport and storage mechanisms by phaeochromocytoma/PG cells, even though SRS might be considered to supplement ^{123}I-MIBG in suspicious metastatic phaeochromocytomas [66].

Several PET radiopharmaceuticals have been proposed, tracing the catecholamine pathway: FDOPA, its metabolite FDA [67], and ^{11}C-hydroxyephedrine [68, 69]. FDOPA PET imaging of phaeochromocytoma was proposed by Hoegerle et al. in 2002 [70]. FDOPA PET, ^{123}I-MIBG scintigraphy and MRI were performed in 14 consecutive patients suspected of having phaeochromocytomas [5 sporadic and 9 with von Hippel-Lindau (VHL) syndrome]. Both FDOPA PET and MRI detected 17 phaeochromocytomas (11 solitary, 3 bifocal; 14 adrenal, 3 extra-adrenal). Sensitivity was 100 % for FDOPA PET vs 71 % for ^{123}I-MIBG scintigraphy, and specificity was 100 % for both procedures.

Since then, several studies have been published [17, 70–87] (Table 2) and also European Association of Nuclear Medicine (EANM) guidelines [80]. A recent meta-analysis of 11 studies comprising 275 patients with suspected PG [81] found that pooled sensitivity of FDOPA PET(/CT) in detecting PG was 91 % (patient based) and 79 % (lesion based). The pooled specificity of FDOPA PET(/CT) was 95 % for both patient-based and lesion-based analyses. FDOPA PET(/CT) seems to be accurate in both adrenal [17, 70–72] or extra-adrenal [73, 75–77], sympathetic [70–72, 74] or parasympathetic [73, 75–77], functioning [74] or non-functioning [71, 73, 76] and metastatic or non-metastatic PG [75, 79, 82] or VHL [70, 83, 84] PG.

When compared to ^{123}I-MIBG [74, 77, 79], SRS [76], MRI [73, 74] or CT [74], FDOPA had the best diagnostic performance. In particular FDOPA is very sensitive for detecting head and neck PG, usually derived from parasympathetic ganglia [73, 76]. In contrast, no MIBG uptake is detected when expression of vesicular monoamine transporter 1 is lacking [77].

In the series of Charrier et al. [76], FDOPA PET detected significantly more cervical than abdominal lesions (97 vs 67 %); in two patients with the succinate dehydrogenase subunit D (SDHD) mutation, FDOPA PET missed five abdominal
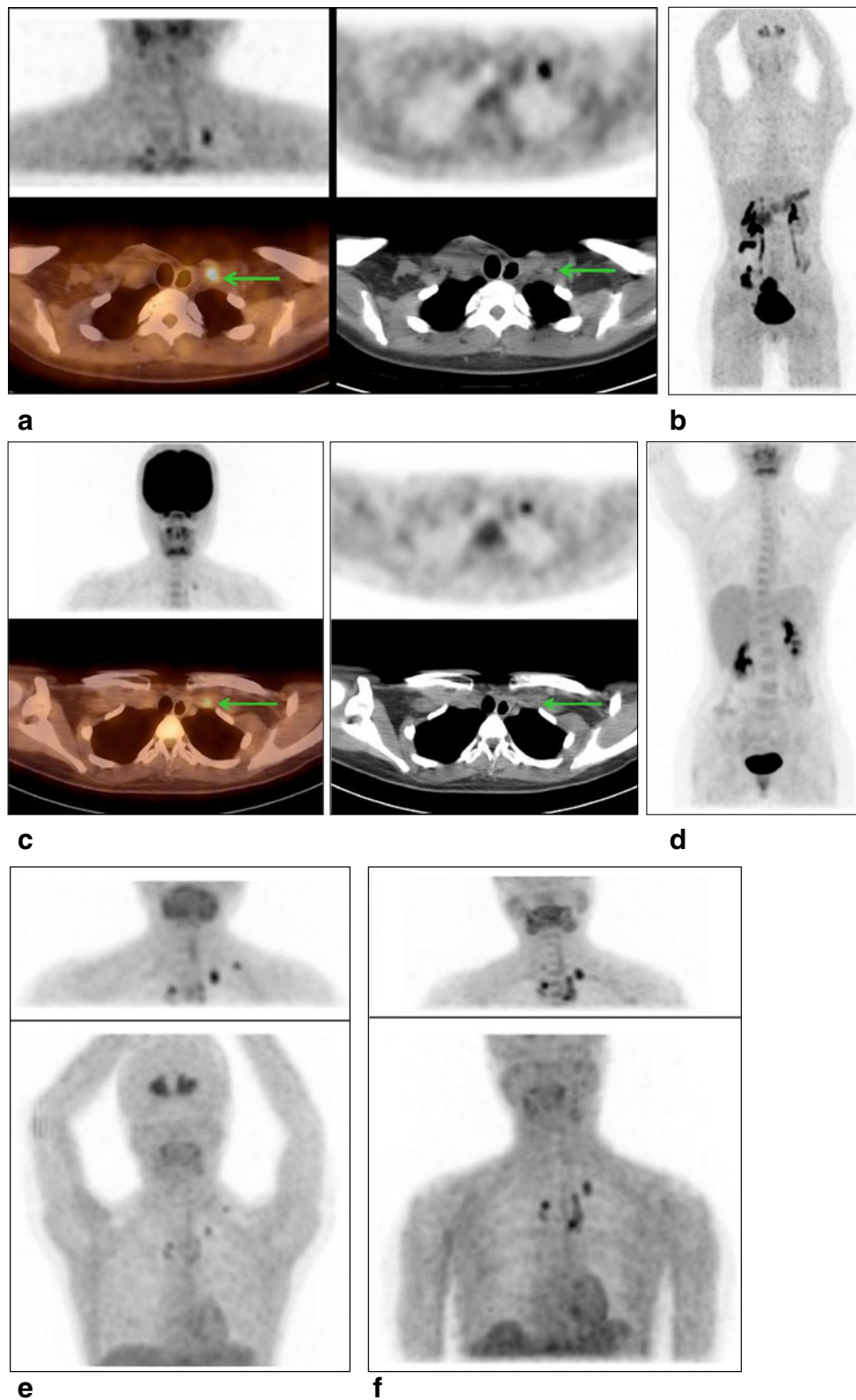
PG lesions, which were detected by the combination of SRS, ^{131}I-MIBG and FDG. In other studies, SDHD mutation was associated with good FDOPA patient-based detection rate: eight of ten [73], five of six [77], seven of seven [78], eight of eight [84] and four of four [82], overall 91 %.

The comparison with FDG or FDA should be performed according to PG aggressiveness (Fig. 2) and genetic

◄ **Fig. 1** MTC treated by total thyroidectomy and lymph node dissection. **a–b** The patient presented with an occult biochemical recurrence 1.5 years later [serum calcitonin (CTN)=1,130 ng/l, carcinoembryonic antigen (CEA) =46 μg/l] and was referred to FDOPA PET/CT. On the early images after injection (**a**), a clear focus was visible, corresponding on CT to a left lymph node in the left upper mediastinum, with smaller and less intense contralateral foci. But the foci were no longer visible 1 h later on the whole-body acquisition (**b**) and the examination was considered as doubtful. **c–e** Another 1.5 years later, the markers were still rising (CTN=2,400 ng/ml, CEA =59 μg/l) and the patient was referred for FDG and FDOPA PET/CT prior to surgical exploration. On FDG PET/CT, 1 h after injection, a faint uptake (SUV$_{max}$ =1.8) was visible by the left mediastinal lymph node (the most intense FDOPA uptake 1.5 years before) (**c**) but no other lesion (**d**). On FDOPA PET/CT (**e**), the left mediastinal focus took up FDOPA (SUV$_{max}$ =2.9) together with several other foci: one left supraclavicular focus and one upper thoracic focus on the left side and two foci in the right upper mediastinum. Their intensity decreased after 1 h. The dissection and histological examination of the left supraclavicular region found two metastatic lymph nodes, 8 and 5 mm in size. CTN levels dropped to 1,600 ng/l. **f** Nineteen months later, another FDOPA PET was performed for restaging prior to surgery. With the exception of the left supraclavicular focus which had been resected, all other foci were viable, and their uptake at 1 h was now as intense as on the early images. This observation illustrates the importance of early image acquisition after FDOPA injection for early detection of metastatic MTC and the better performance of FDOPA as compared to FDG in a slow-growing form of MTC

mutations. In 2009 Timmers et al. published a comparative study of 52 patients [82] using FDOPA PET, ^{123}I-MIBG scintigraphy, FDA PET/CT and FDG PET/CT. It should be noted that FDOPA imaging was performed with a PET only machine of a former generation than PET/CT used for the two other PET tracers. In 15 patients with succinate dehydrogenase subunit B (SDHB) mutation, FDA and FDG had a higher overall lesion-based sensitivity (82 and 83 %) than ^{123}I-MIBG (57 %) and FDOPA (20 %). In 13 patients without SDHB mutation, including 4 patients with SDHD mutation, FDOPA had the best lesion-based sensitivity (93 %), followed by FDA (76 %), ^{123}I-MIBG (59 %) and FDG (62 %).

As somatostatin receptors are expressed by 73 % of phaeochromocytomas and 93 % of PG [85], SRS is an alternative. In the limited comparative studies, its sensitivity was less than that of FDOPA but greater than that of ^{123}I-MIBG, in particular in head and neck PG [76, 78] or to detect metastatic sites of malignant phaeochromocytoma [66]. Concordantly, the superiority of SRPET over ^{123}I-MIBG SPECT to pick up head and neck PG lesions and bone metastases has been confirmed recently in a series of 15 patients [86]. For the moment, there is no comparative study between FDOPA and SRPET(/CT) in this context.

Concerning the impact of FDOPA PET on the management of PG patients, the rate of change in patient management was, in our series, 3/24 (12 %) overall and 3/15 (20 %) in proven phaeochromocytoma, leading to pertinent decisions [87]. In the prospective study by Fiebrich et al., FDOPA PET influenced treatment decisions in 14/48 patients (29 %) [74].

In conclusion, a strategy of examinations in the diagnostic workup of PG/phaeochromocytoma could be to perform FDOPA PET/CT as first-line examination, except in patients with clinically aggressive forms or with SDHB mutation in whom FDG (or FDA if available) should be preferred.

Well-differentiated carcinoid tumours of the digestive tract of a midgut origin

Endocrine tumours of the gastrointestinal tract are characterised by a great heterogeneity. The midgut carcinoid, originating from enterochromaffin Kulchitsky cells in the crypts of Lieberkühn in the small intestine, has a relatively high tendency to metastasise via local lymph nodes to the liver; in this context, most patients present with carcinoid syndrome, including symptoms of flushing, diarrhoea, bronchoconstriction and right-sided heart failure caused by overproduction of substances such as serotonin and tachykinins. Serotonin is produced by the carcinoid tumour cells. Concerning the performance of SPECT radiopharmaceuticals, by pooling the results of two comparative series, the patient-based detection rate was 64/71 =90 % for SRS vs 48/71 =68 % for MIBG [62, 88]. In one series aggregating the results of carcinoid tumours of various origins, the detection rate was also better for SRS: 67 vs 50 % for ^{123}I-MIBG [89].

The initial case with FDOPA imaging in a NET reported by Hoegerle et al. in 1999 [90] was a patient with metastasising carcinoid in whom various imaging procedures were not successful in detecting the primary tumour. Due to the importance of primary tumour proof for potential curative surgical therapy, FDOPA PET was performed that enabled localisation of a potential primary tumour in the ileum. Moreover, in addition to the known abdominal lymph node and liver metastases, it detected a mediastinal lymph node metastasis and a pulmonary metastasis.

Hoegerle et al. [91] subsequently demonstrated, in 16 patients with gastrointestinal carcinoid tumours, that lesion-based sensitivity was 65 % for FDOPA PET, better than 57 % for SRS and 29 % for FDG PET; however, the midgut origin of all tumours was not ascertained.

Possible detection of metastatic lesions with FDG was reported in 8/11 patients with NET of midgut or unknown origin [92]; SRS detected NET in 10/11 patients. The detection rate of FDG PET was less in another series [93]: metastatic NET of the small intestine was visible in only one of four cases.

In 24 patients with abdominal carcinoid tumours and biochemical proof of increased serotonin metabolism, per-patient analysis showed sensitivities of 100 % for 5-HTP, 96 % for FDOPA, 86 % for SRS and 96 % for CT [18]. Per-lesion analysis revealed sensitivities of 78 % for 5-HTP PET, 89 %

Table 2 FDOPA and comparators in phaeochromocytoma and/or paraganglioma: studies with a standard of truth

Reference	No. of patients	FDOPA imaging technique	Performance of FDOPA imaging	Comparator(s) and performance(s)
Hoegerle et al. (2002) [70].	14 patients with suspected phaeo, 8 controls	PET	Se patient based 14/14=100 %	^{123}I-MIBG Se 9/12=75 %
			Sp patient based 8/8=100 %	
			Se lesion/site based 17/17=100 %	^{123}I-MIBG 10/14=71 %
			Sp lesion/site based 25/25=100 %	^{123}I-MIBG 22/22=100 %
Montravers et al. (2008) [87]	24 patients with suspected or recurrent phaeo	PET or PET/CT	Se patient based 10/11=91 %	
			Sp patient based 14/14=100 %	
Taïeb et al. (2008) [75]	9 patients: 5 with phaeo, 4 with PG	PET/CT	Se patient based 9/9=100 %	FDG PET/CT 8/9=89 % SRS 4/5=80 % ^{131}I-MIBG 6/8=75 %
Fiebrich et al. (2009) [74]	48 patients with catecholamine excess	PET	Se patient based 43/48=90 %	^{123}I-MIBG 31/48=65 % CT/MRI 32/48=67 %
			Se lesion based 91/124=73 %	^{123}I-MIBG 60/124=48 % CT/MRI 55/124=44 %
Imani et al. (2009) [71]	25 patients with suspected or known phaeo	PET (11 patients) PET/CT (14 patients)	Se patient based 11/13=85 %	
			Sp patient based 13/13=100 %	
Kauhanen et al. (2009) [72]	25 patients: 16 for detection and staging phaeo, 9 for restaging phaeo	PET/CT	Staging Se patient based	
			5/5=100 % Sp patient based 11/11=100 % Restaging Se patient based 5/5=100 % Sp patient based 3/4=75 %	
Timmers et al. (2009) [82]	53 patients with known or suspected PG, including: 15 with SDHB mutation 13 without SDHB mutation	PET	Se lesion based Non-metastatic PG 21/26=81 %	^{123}I-MIBG 20/26=78 % FDA PET/CT 20/26=78 % FDG PET/CT 23/26=88 %
			Metastatic PG 96/211=45 %	^{123}I-MIBG 106/187=57 % FDA PET/CT 161/211=76 % FDG PET/CT 157/211=74 %
			SDHB mutation 25/126=20 %	^{123}I-MIBG 60/106=57 %

Table 2 (continued)

Reference	No. of patients	FDOPA imaging technique	Performance of FDOPA imaging	Comparator(s) and performance(s)
				FDA PET/CT 103/126=82 %
				FDG PET/CT 105/126=83 %
			Without SDHB mutation	
			Se 79/85=93 %	^{123}I-MIBG 48/81=59 %
				FDA PET/CT 65/85=76 %
				FDG PET/CT 53/85=62 %
Fottner et al. (2010) [77]	30 patients:	PET	Se patient based	
	24 with catecholamine excess		24/25=96 %	^{123}I-MIBG 20/25=80 %
	5 with adrenal incidentaloma		SDHB mutation 2/6=33 %	^{123}I-MIBG SDHB mutation 2/6=33 %
	1 with SDHD mutation		SDHD mutation 5/6=83 %	^{123}I-MIBG SDHD mutation 3/6=50 %
			Se lesion based	
			Se 63/64=98 %	^{123}I-MIBG 34/64=53 %
				CT/MRI Se 35/64=55 %
			Sp lesion based	
			63/63=100 %	Sp 31/34=91 %
Luster et al. (2010) [17]	25 patients with suspected phaeo	PET/CT	Se patient based	
			Staging 8/8=100 %	
			Restaging Se 7/7=100 %	
			Sp patient based	
			Stading 2/2=100 %	
			Restaging Sp 7/8=88 %	
Charrier et al. (2011) [76]	25 patients with known or suspected non-metastatic extra-adrenal PG	PET/CT	Se patient based	
			22/23=96 %	SRS 17/23=74 %
			Se lesion based	
			39/45=87 %	SRS 23/45=51 % p<0.001
			Se H&N or thoracic lesions	
			29/30=97 %	SRS 20/30=67 %
			Se abdominal lesions	
			10/15=67 %	SRS 3/15=20 %
King et al. (2011) [78]	10 patients with H&N PG:	PET/C	Se patient based	
	7 SDHD mutation		10/10=100 %	CT/MRI 10/10=100 %
	3 SDHB mutation			FDG PET/CT 8/10=80 %
				FDA PET/CT 4/10=40 %
				^{123}I-MIBG 4/10=40 %
				SRS 8/9=89 %
			Se lesion based	
			26/26=100 %	CT/MRI 21/26=81 %
				FDG PET/CT 20/26=77 %
				FDA PET/CT 12/26=46 %
				^{123}I-MIBG 8/26=31 %
				SRS 16/25=64 %
Rufini et al. (2011) [79]	12 patients with known or suspected recurrent PG	PET/CT	Se patient based	
			Se 12/12=100 %	^{123}I-MIBG Se 9/12=75 %
			Se lesion based	
			Overall	
			347/353=98 %	^{123}I-MIBG 136/353=38 %

Table 2 (continued)

Reference	No. of patients	FDOPA imaging technique	Performance of FDOPA imaging	Comparator(s) and performance(s)
			Bone	
			285/287	^{123}I-MIBG 97/287
			Soft tissue	
			62/66=94 %	^{123}I-MIBG 39/66=59 %
			Lymph nodes	
			25/29=86 %	^{123}I-MIBG 18/29=62 %
			Liver	
			25/25=100 %	^{123}I-MIBG 18/25=72 %
Rischke et al. (2012) [84]	101 patients with suspected or proven phaeo or PG: 68 proven	PET/CT	Se patient based	
			Overall	
			63/68=92 %	
			VHL mutation 17/19=89 %	
			SDHB mutation 10/12=83 %	
			SDHD mutation 8/8=100 %	
			Other mutation 3/3=100 %	
			No mutation 20/20=100 %	
			Sp patient based	
			29/33=88 %	
			Se lesion based	
			Overall	
			180/189=95 %	
Overall	258 patients with phaeo or PG		Se patient based	
	89 patients without		243/258=94 % (95 % CI 91.4–97.1)	^{123}I-MIBG 79/115=69 % (95 % CI 60.2–77.1)
			Sp patient based	
			84/89=94 % (95 % CI 87.4–98.2)	
			Se lesion based	
			700/866=81 % (95 % CI 78.4–83.4)	^{123}I-MIBG 314/670=47 % (95 % CI 43.1–50.7)
			Sp lesion based	
			Sp 88/88=100 % (95 % CI 95.9–100)	^{123}I-MIBG 53/56=95 % (95 % CI 85.1–98.9)

CI confidence interval, *FDA* ^{18}F-fluorodopamine, *H&N* head and neck, *phaeo* phaeochromocytoma, *PG* paraganglioma, *SDHB* succinate dehydrogenase subunit B, *SDHD* succinate dehydrogenase subunit D, *Se* sensitivity (or patient-based detection rate when all patients are diseased). *Sp* specificity, *SRS* somatostatin receptor scintigraphy using ^{111}In-pentetreotide, *VHL* von Hippel-Lindau

for 5-HTP PET/CT, 87 % for FDOPA PET, 98 % for FDOPA PET/CT, 49 % for SRS, 73 % for SRS SPECT/CT and 63 % for CT alone. FDOPA detected significantly more lesions than SRS and than 5-HTP.

This very elective FDOPA uptake by midgut NET made it possible, in three patients, to differentiate on PET between metastases of NET and a second primary malignancy, an FDG-positive adenocarcinoma [94]. Metachronous cancers frequently develop in patients with small intestine carcinoid tumours (29 % according to Amin et al. [95]) and deserve full staging and treatment. A similar case is reported on in Fig. 3.

In a series of 77 patients with digestive NET [96], the large majority (82 %) being of midgut origin, FDOPA uptake on PET reflected tumour load. Patient whole-body metabolic tumour burden determined on FDOPA PET/CT was correlated with urinary serotonin, urinary and plasma 5-hydroxyindoleacetic acid (5-HIAA), urinary norepinephrine, epinephrine, dopamine and plasma dopamine, but not with serum chromogranin A (CgA).

Comparison with SRPET is currently only available in a few cases. In the series of Ambrosini et al., PET/CT results were concordant in two cases with multiple lymph node and/or liver lesions [57], FDOPA showing more lesions in
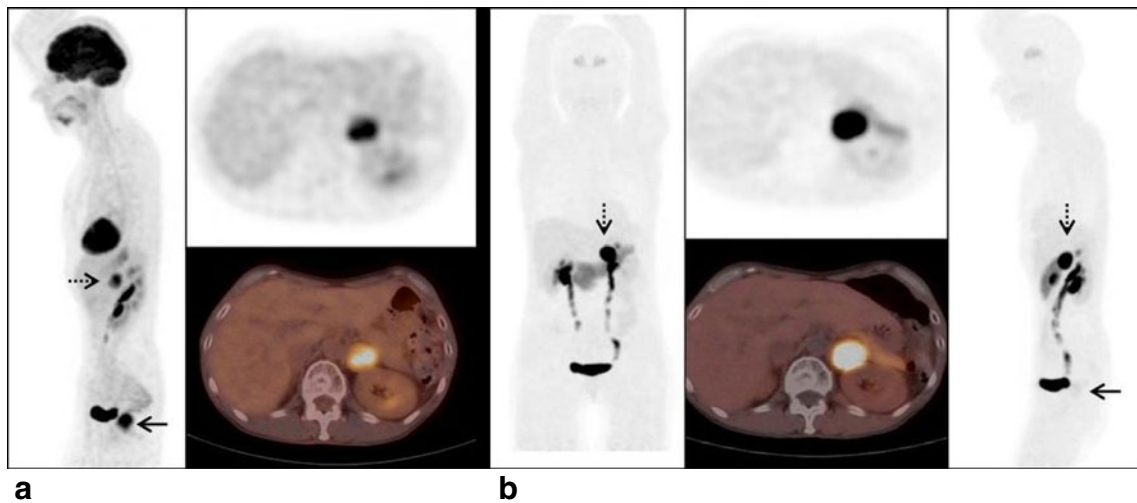
Fig. 2 *Right block of images* FDOPA PET/CT: anterior and left lateral maximum intensity projection, transverse slice. *Left block* corresponding FDG PET/CT images. FDOPA PET/CT was performed for characterising a left adrenal tumour (*dashed arrow*) discovered incidentally on FDG PET/CT performed for staging a squamous cell carcinoma of the anal canal (*full arrow*) in an asymptomatic patient. As the adrenal tumour took up both FDOPA and FDG, it was interpreted as an aggressive phaeochromocytoma. This was confirmed on histological examination. This observation illustrates the increase in specificity brought by FDOPA for characterising NET

one case and SRPET in the other one. In the series of Haug et al., four NET in patients with serotonin levels >700 ng/ml originated from the ileum, and all were FDOPA positive and SRPET positive [97]. An interim analysis of the on-site readings of a prospective study that we are currently performing demonstrated that, in 14 patients with a carcinoid tumour of the ileum, the patient-based sensitivity was 100 % for both FDOPA PET/CT and SRPET/CT but FDOPA showed more uptake foci in 8/14=44 % of patients

[98]. In summary, in all 20 patients, both tracers were able to detect lesions of midgut carcinoid NET, FDOPA showing more lesions in 9/20= 45 % of patients and SRPET in 1/20= 5 % of patients.

The rate of change in management was 50 % in our series of 22 patients with histologically documented carcinoid tumour of the ileum, relevant in all cases according to follow-up data [21]. In the series of 16 digestive carcinoid tumours of Hoegerle et al. [91], FDOPA PET resulted in
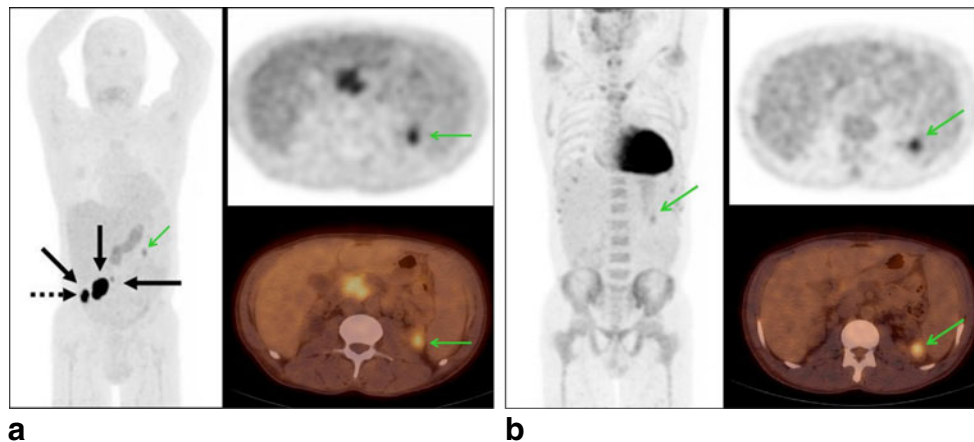

Fig. 3 a–b In a haemodialysed patient candidate for renal grafting, systematic CT discovered a tumour of the terminal ileum evocative of a carcinoid origin with mesenteric locoregional adenopathies, the largest being 35 mm in size. Biopsy of a right iliac adenopathy confirmed a metastatic well-differentiated NET (Ki-67<1 %). FDOPA PET/CT performed for staging showed the primary carcinoid tumour in the terminal ileum (**a** *dotted arrow*) and large lymphadenopathy with two satellite lymph nodes (**a** *black arrows*), but also a focus in the upper left abdomen, SUV$_{max}$ =4.7 (**a, b** *green arrow*) corresponding on CT to a dense content in a renal cyst. **c** FDG PET/CT was performed to better characterise the renal anomaly that took up FDG (**c** *green arrow* on the transverse slice) with a somewhat lower intensity than FDOPA (SUV$_{max}$ = 3.9). As expected, the metastatic carcinoid tumour in the right abdomen did not take up FDG (**c**). Thus the renal cystic lesion was probably not of a carcinoid origin. A CT-guided biopsy of the renal lesion was performed and histology revealed a renal carcinoma. This observation illustrates the ability of FDOPA to detect carcinoid tumours with low aggressiveness, but also renal carcinomas, and the synergy between FDOPA and FDG PET/CT

modification or even complete change in therapeutic strategy in 31 % of cases.

In conclusion, using FDOPA PET/CT as the first-line functional imaging modality for the management of digestive NET originating from midgut allows small lesions to be detected and corresponds to its MA [18, 20, 91, 99] (Table 3). FDOPA imaging induced relevant changes in patient management [21, 91]. Its superiority over SRS has been confirmed by several teams. SRPET appears to be a competitor, although it showed less foci in some patients; dedicated comparative studies are currently lacking. With FDG PET, very limited results have been reported in midgut NET [91–93]; FDG is able to show some metastatic lesions of intestinal NET, but a significant FDG uptake in this context should also be a warning sign of a metachronous "common" cancer [94].

Neuroendocrine tumours of the digestive tract of hindgut origin (transverse and left colon and rectum)

Hindgut carcinoids metastasise in about 3–5 % of cases and rarely present hormonal symptoms or elevation of urinary-5-HIAA despite the content of peptides and hormones. Globally, these NET are more aggressive and more often poorly differentiated than NET originating from midgut [100].

To the best of our knowledge, no study with FDOPA has been reported in this NET; only two FDOPA-positive SRS-positive cases were reported in the series of Hogerle et al. [90] and three FDOPA-negative SRPET-positive cases in patients with serotonin levels <200 ng/ml in the series of Haug et al. [97]. The patient-based detection rate was 5/6 for FDG vs 4/6 with SRS in the study of Binderup et al. [62] and 5/6 with SRS in the study of Ezziddin et al. [88], MIBG being ineffective in both series (2/12=17 %). Case reports describe FDG imaging and treatment monitoring in aggressive metastatic NET, also referred to as small cell colorectal cancer [101, 102].

In conclusion, in cases of NET tumours of the rectum or the transverse and left colon, FDG and/or SRPET are able to localise the lesions, even if evidence is currently limited about the impact of the examination.

Endocrine pancreatic tumours (except hyperinsulinism in infants), NET of the stomach or the duodenum

Endocrine pancreatic tumours (EPT) are part of foregut NET and include insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas and non-functioning NET. In malignant tumours, mixed syndromes are common due to multiple hormone production from the tumours. In about one third of EPT, the patients present no hormonal symptoms, bearing a non-functioning NET. EPT can also be part of type I multiple endocrine neoplasia (MEN-I)

syndrome, in which multiple pancreatic tumours are almost always found. Concerning the performance of SPECT radiopharmaceuticals, by pooling the results of 3 comparative series, the patient-based detection rate was 47/52 =90 % for SRS vs 17/52 =33 % for MIBG [62, 88, 89].

Only 11/22=50 % of the EPT could be detected with ^{11}C-L-DOPA; in 2 additional patients, CT enabled detection of tumours not detected on PET [103]. We reported concordant results with FDOPA in 10 EPT [20]: poor patient-based sensitivity of 2/8=25 %, contrasting with a better sensitivity of SRS: 6/8=75 %. Concerning other radiopharmaceuticals for SPECT, by pooling the results of 3 comparative series in EPT, MIBG had a low patient-based detection rate of 11/52= 21 % vs 47/52 =90 % for SRS [62, 88, 89]. ^{111}In-glucagon-like peptide 1 (GLP-1) receptor scintigraphy has been proposed specifically for insulinoma [104].

The article of Koopmans et al. in 2008 [18] included 23 patients with pancreatic islet cell tumours; 39 % of patients had biochemical proof of increased serotonin metabolism. Patient-based sensitivity was 100 % for 5-HTP PET, 89 % for FDOPA PET, 78 % for SRS and 87 % for CT. Per-lesion analysis revealed sensitivities of 67 % for 5-HTP PET, 96 % for 5-HTP PET/CT, 41 % for FDOPA PET, 80 % for FDOPA PET/CT, 46 % for SRS, 77 % for SRS SPECT/CT and 68 % for CT alone. Although 5-HTP PET/CT was superior to FDOPA PET/CT in islet cell tumours, ^{11}C-5-HTP cannot be produced and delivered for routine use as easily as FDOPA. In contrast with our results, FDOPA PET/CT had better sensitivity than SRS, even performed with SPECT/CT fusion.

Insulinoma may constitute an indication for FDOPA, as the sensitivity of SRS has been reported to be limited. Currently, only small series have been reported. The detection rate was 9/10=90 % in the series of Kauhanen et al. [105], but another preliminary study reported a poor detection rate [106]: in 5 adults with hyperinsulinism, no tumour was detected with FDOPA while CT was positive in 4 cases; the only FDOPA detection occurred in 1 child with multiple NET MEN-I.

FDOPA PET was compared with SRPET in very small series. Its performance was equal to that of ^{68}Ga-DOTATOC in four EPTs reported by Putzer et al. [107]. In the series of Ambrosini et al., the per-patient detection rate was 5/8 for FDOPA vs 8/8 for ^{68}Ga-DOTANOC [57] which showed more foci in 4 of the 5 FDOPA-positive patients. In another series of five EPTs, FDOPA was positive in three cases whereas SRPET was positive in all cases [97]. Since FDOPA has a limited sensitivity for most types of EPT and a good one for midgut digestive NET, in series mixing several types of NET, its overall sensitivity and the result of comparison with SRPET depend on the relative proportions of those different types of NET.

Table 3 FDOPA and comparators in digestive carcinoid tumours: studies with a standard of truth

Reference	No. of patients	Performance of FDOPA imaging	Comparator(s) and performance(s)
Hoegerle et al. (2001) [91]	16/17 patients with confirmed gastrointestinal carcinoid tumours	Se patient based	
	92 sites	11/16=69 %	SRS 13/16=81 %
			FDG 7/16=44 %
			CT/MRI 12/16=75 %
		Se site based	
		Primary tumour	
		FDOPA 7/8=88 %	SRS 4/8=50 %
			FDG 2/8=25 %
			CT/MRI 7/8=88 %
		LN metastases	
		FDOPA 41/47=87 %	SRS 27/47=57 %
			FDG 14/47=30 %
			CT/MRI 47/47=100 %
		Organ metastases	
		FDOPA 12/37=32 %	SRS 21/67=57 %
			FDG 11/37=30 %
			CT/MRI 37/37=100 %
		Overall site based	
		60/92=65 %	SRS 52/92=57 %
			FDG 29/92=27 %
			CT/MRI 91/92=99 %
		FDOPA impact on patient management: 30 %	
		CT/MRI>FDOPA>SRS>FDG	
Koopmans et al.(2008) [18]	24 patients with carcinoid tumour	Se patient based	
	371 lesions	FDOPA 23/24=96 %	5-HTP 24/24=100 %
			SRS 18/24=86 %
			CT 23/24=96 %
		Se lesion based	
		PET 322/371=87 %	5-HTP 288/371=78 %
		PET+CT 364/371=98 %	5-HTP+CT 330/371=89 %
			SRS 182/371=49 %
			SRS+CT 271/371=73 %
			CT 234/371=63 %
		FDOPA & 5-HTP detected more lesions than SRS ($p<0.001$)	
Montravers et al. (2006) [20]	18 examinations in 16 patients with midgut carcinoid tumour	Se patient based	
		FDOPA 13/14=93 %	SRS 11/14=78 %
		Sp patient based	
		FDOPA 3/4=75 %	SRS 2/3=67 %
Yakemchuk et al. (2012) [99]	18 patients with midgut carcinoid tumour	Se patient based	
	189 sites	20/21=95 %	SRS 19/21=90 %
	183 lesions		CT 19/21
		Se site based	
		53/56=95 %	SRS 34/56=61 %
			CT 37/56=66 %

Table 3 (continued)

Reference	No. of patients	Performance of FDOPA imaging	Comparator(s) and performance(s)
		FDOPA vs SRS and/or CT, $p<0.001$ Se lesion based	
		175/183=96 %	SRS 92/183=50 %
			CT 126/183=69 %
		FDOPA vs SRS and/or CT, $p<0.001$ Sp site based	
		132/132=100 %	SRS 132/133=99 %
			CT 132/135=98 %
		2/21=10 % major impact on patient management 10/21=48 % minor impact on patient management	
Overall	76 patients	Se patient based	
		68/76=89 % (95 % CI 80.3–95.3)	SRS 60/75=80 % (95 % CI 69.2–88.4)
			CT/MRI 54/61=89 % (95 % C: 77.8–95.3)
		Se site based	
		113/148=76 % (95 % CI 76.3–83.2)	SRS 86/148=58 % (95 % CI 50.2–66.0)
			CT/MRI 128/148=86 % (95 % CI 81–92)
		Se lesion based	
		539/554=97 % (95 % CI 96.0–98.6)	SRS 274/554=49 % (95 % CI 45.3–53.7)
			CT/MRI 360/554=65 % (95 % C: 61–69)

LN lymph node, *5-HTP* [11] C-5-hydroxytryptophan PET, *CI* confidence interval, *Se* sensitivity, *Sp* specificity, *SRS* somatostatin receptor scintigraphy using [111] In-pentetreotide

No series have been identified concerning stomach or duodenal NET, also part of foregut digestive NETs, and only a few cases in larger series: patient-based sensitivity of 1/4=25 % for FDOPA vs 3/5=75 % for SRS [20] or of 2/4=50 % for FDOPA vs 3/4=75 % with SRPET (pooling results of studies [57], [97] and [107]), SR-based imaging usually showing more foci.

In the case of an aggressive form of well-differentiated NET with Ki-67 >10 %, the first-line tracer should be FDG: in 18 patients (15 with foregut NET), FDG patient-based sensitivity was 100 % vs 83 % for SRS, and FDG PET detected more lesions than SRS in 78 % of cases [108]. When no selection was made on Ki-67 value, the detection rate in 29 patients was 79 % for FDG and less than 90 % for SRS [62].

In conclusion, in cases of differentiated EPT, SRPET is the first-line examination, except if Ki-67 >10 % favours FDG PET. If negative, FDOPA can be useful, in particular in gastric or duodenal NET as well as in some cases of positive SRPET or FDG PET when there is a doubt about the nature of a positive focus: FDOPA is more tumour specific than the somatostatin analogues or FDG which are taken up by leucocytes in inflammatory lesions.

Congenital hyperinsulinism in infants

Although insulinoma, a digestive NET generally of a benign nature, induces hyperinsulinism, congenital hyperinsulinism (CHI) is a specific clinical setting, as clustered beta-cell hyperplasia is found in the resectable cases, rather than a definite tumour. Although this indication does not strictly belong to oncology, the excellent performance of FDOPA will be briefly summarised.

In infants with CHI, which results in life-threatening hypoglycaemia, the aim of imaging is to localise focal hyperplasia

of beta cells in the pancreas: hyperinsulinism with focal lesion (s) can revert by selective surgical resection, in contrast to the diffuse form, which requires subtotal pancreatectomy when resistant to medical treatment.

In the initial study by Ribeiro et al. on 15 CHI children (aged 1–14 months) [11], FDOPA PET showed an abnormal focal pancreatic uptake in 5 patients who then underwent a limited pancreatic resection that was followed by a complete clinical remission. A diffuse pancreatic uptake was observed in ten patients, four of whom underwent surgical resection that confirmed FDOPA PET results: the abnormal beta cells were gathered in small clusters, scattered in the whole pancreas. In contrast, MRI performed in six infants showed no anomaly.

These very promising results were confirmed in larger series by the same team and by many others [109–114] (Fig. 4). In a recent German study [114], FDOPA PET/CT with multiphase contrast media protocols was performed in 135 CHI patients. All the foci were excised on the basis of FDOPA PET/CT images and 87–91 % of the operated patients could be completely healed.

Two meta-analyses have been recently published. An Italian team concluded that the pooled sensitivity and specificity of FDOPA PET(/CT) in differentiating between focal and diffuse CHI were 89 and 98 %, respectively [115]. An American team aimed to compare the diagnostic performance of FDOPA PET, pancreatic venous sampling (PVS) and selective pancreatic arterial calcium stimulation with hepatic venous sampling (ASVS) in diagnosing and localising focal CHI [116]. FDOPA PET was superior in distinguishing focal from diffuse CHI [summary diagnostic odds ratio (SDOR)= 73.2], compared to PVS (SDOR= 23.5) and ASVS (SDOR= 4.3). Furthermore, it localised focal CHI in the pancreas more accurately than PVS and ASVS (pooled accuracy 82 vs 76 and 64 %, respectively).

In conclusion, the results of recently published large series are in accordance with the initial ones: FDOPA PET (/CT) is of major utility to select those infants for surgery and shortens the intervention by guiding the surgical exploration of the pancreas.

"Carcinoids" or "endocrine small cell" or "oat cell" tumours of other organs

Carcinoid tumours can be observed in several others organs. Probably due to the urinary excretion of radiopharmaceuticals, their use seems limited in NET of the kidney or the urinary bladder to detection and treatment follow-up of metastases, as reported by Iagaru et al. using FDG PET [117]. The published case reports with nuclear imaging are focused on two sites, thymus and prostate, but none reported the use of FDOPA.

In summary, thymic NETs are aggressive and diagnosed at an advanced stage. FDG was able to accurately stage one patient with lymph node and bone metastases, which were not visible either on MIBG or on bone scintigraphies [118], and to restage a recurrent thymic NET with multiple bone metastases which were not visible on bone scintigraphy [119]. In contrast, SRPET did not show any thymic NET in the four cases of another series [120]. These preliminary results seem somewhat discrepant with a foregut origin currently accepted for thymus NET.

Small cell carcinoma of the prostate (SCCP) is very aggressive, metastasises early and does not respond to most chemotherapy regimens. In approximately 50 % of cases of prostate cancer, tumours are a combination of small cell carcinoma and androgen-sensitive adenocarcinoma. Our team performed FDOPA PET in four patients that did not show the NET contingent of the prostate cancer which was

Fig. 4 FDOPA PET/CT: maximum intensity projection, transverse slice and coronal slice. Search for focal hyperplasia of pancreatic beta cells in an infant with hyperinsulinism. FDOPA PET/CT localised a focus in the tail of the pancreas which was resected. Histological examination confirmed clustered beta-cell hyperplasia and the infant became euglycaemic
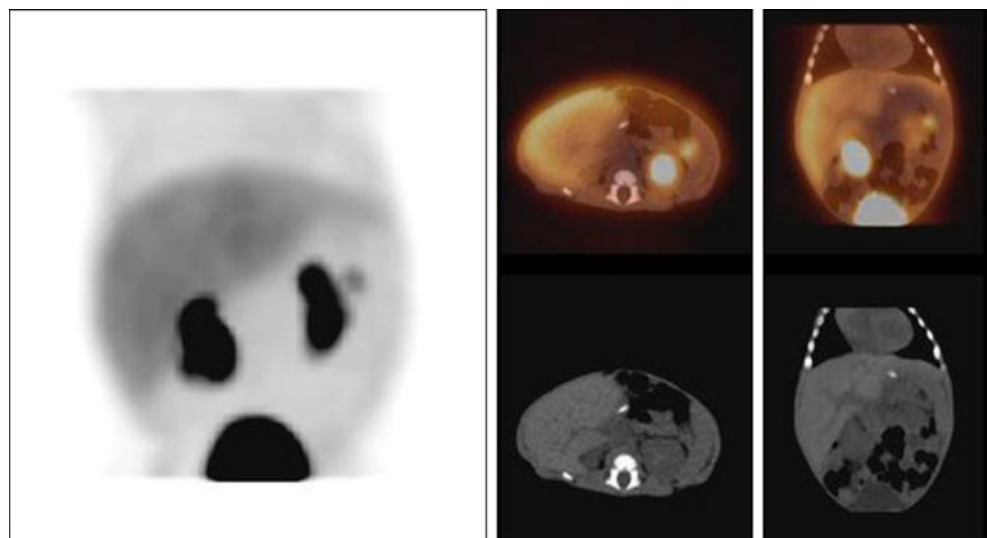
either demonstrated at histological examination (one case taking up FDG) or suspected on high serum levels of CgA. In 2002, Spieth et al. [121] reported in one SCCP patient that SRS was more sensitive than bone scintigraphy to detect metastatic foci. More recently, the use of FDG PET has been reported in case reports for detecting SCCP [122–124] and monitoring therapy [125].

In conclusion, in those aggressive NETs, FDG PET/CT seems to be the best first-line examination.

Detection of unknown primary NET: NET metastases of unknown origin, ectopic hormone secretion, or suspicion of NET or of MEN

Concerning NET metastases of unknown origin ("CUP-NET"), the localisation of the primary tumour is important to optimise patient management [126]. The choice of the best tracer depends on the most probable primary tumour and on its aggressiveness. As FDG was superior to SRS to detect metastatic NET, in correlation with Ki-67 [127], FDG could be tried first in CUP-NET if Ki-67 is >10 %. High levels of a biochemical marker may provide guidance: serotonin or urinary 5-HIAA or catecholamine derivates or calcitonin favour using FDOPA [96, 97]. Immunohistochemistry may also help. The presence of CDX-2 in metastases had a specificity of 100 % and a sensitivity of 40 % for a midgut primary NET, favouring FDOPA imaging [128]. The presence of Islet 1 in metastases had a specificity of 100 % and a sensitivity of 78 % for a primary EPT [128]. PDX-1 was positive in five of five cases of metastatic pancreatic NET and two of two cases of metastatic duodenal NET [129] and TTF-1 was expressed almost only in bronchopulmonary NET [128, 129]. Thus, the presence of those markers favours SRPET. Other markers for immunochemistry of NET have already been described and more will come in future.

As early as 1999, Hoegerle et al. reported a CUP-NET case and the successful delineation of the primary carcinoid tumour with FDOPA PET [90]. Our team reported detection of the primary tumour with FDOPA in 6 of 16 CUP-NET (38 %); in 5 other patients, FDOPA PET upstaged the disease but did not reveal a subsequently confirmed primary NET [21].

Series have also been reported using SRPET. The detection rate of primary tumour was 5/14 [36], 4/4 [97], 3/4 [130], 35/59 [131] and 12/20 [132], overall 59/101=58 %. SRPET could be compared with FDOPA in 4 such patients reported by Haug et al. in 2009 [97]: in 2/4 patients, "FDOPA PET allowed better delineation of the primary tumour, and gave evidence of more metastases, mainly due to higher tumour/non-tumour contrast, which was especially seen in the liver".

Concerning ectopic hormone secretion, PET has been reported in cases of adrenocorticotropic hormone (ACTH) production, which is generally due to lung or carcinoid tumours. In one case, FDOPA successfully detected a BC [56] and in another case a carcinoid of the appendix [133]. In another case, CT demonstrated prominent lymph nodes in the left lung hilum and hyperplastic adrenals but no primary tumour, SRPET/CT was non-contributive, but FDOPA PET/CT localised the metastatic BC [134].

In our centre, eight FDOPA PET/CTs were performed in this setting and two were positive; surgery was performed in one of them, in view of concordance with positive FDG PET/CT, and a thoracic NET was confirmed.

Other cases have been reported using either FDG, the primary NET being a recurrent thymic carcinoid tumour [135], an atypical thymic carcinoid tumour [136] or a hepatic carcinoid tumour [137], or 5-HTP, the primary NET being BC [138], or SRPET that detected a NET of the ileum [139] and a NET in the right sphenoidal sinus [140].

One series of 41 patients has been reported by Zemskova et al. but several imaging modalities were used, not in all patients, with intervals of several months, PET being performed as a second-line examination when others were not conclusive; so, performance of modalities cannot be compared [141]. Patient-based sensitivity was overall 6/13=46 % for FDOPA PET and 7/14=50 % for FDG PET; an important point was the remarkable specificity of FDOPA, in contrast to CT, MRI, SRS and FDG, leading to a very high positive predictive value (PPV). FDOPA PET improved PPV of CT/MRI, while FDG PET did not.

Concerning the localisation of parathyroid adenoma in the case of high serum levels of parathyroid hormone, FDOPA PET was negative in all eight patients reported by Lange-Nolde et al. [142] and could not compete with ultrasonography or with 99mTc-sestamibi scintigraphy. We share the same experience and parathyroid adenomas did not take up FDOPA when present in patients with MEN1.

MEN1 consists of benign or malignant tumours derived from at least two of the following cell types: parathyroid cells, gastrin cells or prolactin-producing pituitary cells. The same negative result was reported with SRPET/CT: of three parathyroid gland adenomas, two were detected by CT only and one remained totally undetected by hybrid imaging [143]. However, in this study, SRPET/CT was able to detect other tumours in 19 patients referred for a MEN1 syndrome, lesion-based sensitivity was 92 % and specificity 93.5 %. Not only 60 NET lesions were detected but also 31 benign MEN-associated lesions. A change in management was induced in 9/19=47 % of patients.

MEN2 associates as the main NET tumours MTC and phaeochromocytoma the detection of which has already been discussed above. FDA [144] or FDOPA could be favoured, as FDG is of little help. In a series, FDG PET could not identify

MTC foci within the thyroid in 14 MEN2A patients, but identified 2 true-positive and 1 false-positive lymph node metastases [145]. In another series, none of the six patients with MEN2A syndrome had a positive FDG PET/CT for MTC [146].

Concerning the detection of NET when only suspected, some data are available in cases of evocative clinical symptoms, or of biological suspicion based on tumour marker levels or of a suspected NET on imaging.

In a comparative study of FDOPA PET/CT and SRS in 61 patients, FDOPA PET/CT correctly identified 32 of 36 patients who actually had a NET, with a sensitivity of 91 %, significantly greater than that of SRS (59 %), and a specificity of 96 vs 86 % for SRS [147]. In 16/61=26 % of the patients, the management was altered as a result of new findings on FDOPA PET/CT.

In a subgroup of 13 patients with suspected NET from a larger series, SRPET had a sensitivity of 4/4=100 % vs. 2/4=50 % for SRS, the specificity being 8/9=89 % for both modalities [148]. In a larger series, 70 patients were examined by SRPET/CT primarily because of the clinical suspicion of NET on the basis of symptoms such as persistent diarrhoea or flushing, 49 patients because of elevated levels of tumour markers and 53 patients because of a mass suggestive of NET [149]. Only one third of the patients included in the study group proved to have a NET, the most frequent localisation of which was the small bowel (10/36=28 %); patient-based sensitivity was 81 % and specificity 90 %. No conclusion can be drawn from the somewhat better sensitivity of FDOPA PET/CT (91 %) [147] vs SRPET/CT (81 %) [149] as those two studies, of a similar sample size, were not comparative; the relatively high frequency of small bowel NET in this setting is concordant with a good performance of FDOPA.

An interesting point is the high proportion of unconfirmed suspicion of NET in the three studies (overall 102/178=57 %). This can be explained by the lack of specificity of the clinical signs or of the aspect of the tumour on conventional imaging; but a selection based on chromogranin-A or on neuron-specific enolase (NSE) serum levels was not more effective: NET was confirmed only in 16/49=33 % of such cases in the series of Haug et al. [149]. Of the 43 patients with elevated levels of chromogranin-A, just 12 (29 %) had histologically proven NET and the diagnostic performance of SRPET was not better in this subgroup of patients. According to our experience, patients are too frequently referred for a sophisticated imaging examination due to a non-specific rise in chromogranin-A levels in relation to proton pump inhibitor treatment [150]. Short-term proton pump inhibitor use (7 days only) results in a significant increase of chromogranin-A levels; proton pump inhibitors need to be discontinued for 2 weeks to fully eliminate their effect on chromogranin-A levels [151]. A simpler alternative is to assay markers which are not affected by this very frequent treatment in patients with digestive disorders; pancreastatin has recently

been proposed [152]. Concerning NSE, not all clinicians are aware of the importance of processing the blood sample: haemolysis or conservation at room temperature result in meaningless high results [153].

In conclusion, FDOPA, FDG and SRPET/CT can detect the primary NET in a significant number of patients with metastatic NET. The sequence of those examinations will be guided by physical signs, serum markers, immunochemistry and also the availability of the tracers at the PET centre. FDOPA and SRPET/CT can detect suspected primary NET, serum markers being useful to choose the first-line examination when both are available, associated infection or inflammation favouring FDOPA. Causes of a non-specific rise in tumour marker serum levels should be considered and ruled out.

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