Clinical Value of ^{18}F-fluorodihydroxyphenylalanine Positron Emission Tomography/Contrast-enhanced Computed Tomography (^{18}F-DOPA PET/CT) in Patients with Suspected Paraganglioma

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Abstract. *Aim: To evaluate ^{18}F-fluorodihydroxyphenylalanine-positron emission tomography/ contrast-enhanced computed tomography (^{18}F-DOPA PET/CT) for the detection of paragangliomas (PARA) without any patient selection, such as genetic predisposition for the development of these tumors, history of metastatic PARA or hormonal status. Patients and Methods: In this retrospective study, 28 consecutive patients (15 women, 13 men; mean age=46.4 years; age range=19-73 years), who were referred to our PET/CT center for the detection of clinically suspected PARA, were included. Final diagnosis was confirmed by histological reports of surgically proven lesions and/or clinical follow-up (including laboratory results and/or PET/CT follow-up). Results: On a per-lesion basis (45 lesions) analysis, there was a sensitivity of 64.3% for CT, 73.8% for PET, 100% for PET/CT and a positive predictive value (PPV) of 93.1% for CT, 96.9% for PET and 100% for PET/CT. On a per-patient basis analysis, the sensitivity, specificity and accuracy for CT was 86.7%, 84.6% and 85.7%, respectively, and, for PET 80%, 100% and 89.3%, respectively, and, for PET/CT 100%. Conclusion: Based on our data, ^{18}F-DOPA PET/CT is a "one-stop diagnostic modality" for the assessment of patients with suspected PARA.*

Paragangliomas (PARA) are rare neuroendocrine tumors, arising from the chromaffin cells of the sympathetic and parasympathetic paraganglia (1, 2). Most are located in the adrenal gland and are called pheochromocytomas, while about 15-20% arise from an extraadrenal site (1, 2). PARA can be found from the base of the skull to the urinary bladder (1, 2). In the thorax and abdomen, most PARA are hormonally active (functioning PARA) and present with symptoms of excess catecholamine secretion. Non-functioning PARA often occur in the head and neck region with the classic clinical manifestation of an enlarging palpable mass (3, 4).

For the diagnosis of PARA, anatomical and functional imaging methods are important because a differentiation between benign and metastatic can only be achieved by detecting metastases or local tumor invasion. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) allow precise anatomical localization of the tumor and provide high sensitivity. Functional imaging modalities with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG), ^{18}F-fluorodeoxy-glucose (^{18}FDG), ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) and ^{68}Ga-DOTA-Tyr(3)-octreotide (68Ga-DOTA-TOC) offer high sensitivity (5-13).

In particular, ^{18}F-DOPA has been proposed as a useful radiopharmaceutical for imaging of catecholamine-secreting tumors. ^{18}F-DOPA was compared to other commonly used functional imaging methods, such as ^{123}I-MIBG scintigraphy

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or ^{18}FDG-PET, in a few studies, and showed a higher sensitivity and specificity for detecting PARA (7, 8, 14). Most ^{18}F-DOPA studies have focussed on selected patients with metastatic PARA or PARA associated with genetic disorders and without distinguishing between adrenal or extraadrenal localization. To our knowledge, no studies have evaluated the usefulness of ^{18}F-DOPA PET/CT in the detection of extraadrenal PARA in unselected patients.

We aimed, in the present study, to evaluate the clinical value of ^{18}F-DOPA PET/contrast-enhanced CT for the detection of clinically suspected extraadrenal PARA, without any patient selection. Additionally, we compared ^{18}F-DOPA PET/ contrast-enhanced CT with ^{18}F-DOPA PET and contrast-enhanced CT.

Patients and Methods

Patients. In our retrospective study, 28 patients (15 women, 13 men; mean age=46.4 years; age range=19-73 years) who were referred to the Medical University of Vienna PET/CT center, between June 2008 and December 2012 for imaging of clinically suspected PARA, were included. In all of our patients, an adrenal lesion was excluded previously by other imaging modalities like ultrasound, CT or MRI. Suspicion of newly presenting or recurrent PARA was based on clinical findings, hormonal analyses or both.

The study was approved by the local Ethics Committee.

Imaging. For all patients, a whole-body PET/CT examination (*i.e.*, from the head to the upper thigh) was performed using a Siemens Biograph 64-row, multi-detector, hybrid PET/CT system (Siemens, Erlangen, Germany). The PET-tracer L-6-[^{18}F] fluoro-3, 4-dihydroxyphenylalanine, [^{18}F]-Fluoro-DOPA was commercially obtained from IASON, Graz, Austria. ^{18}F-Fluoro-DOPA is produced according to a published method of Namavari *et al*. (15, 16). Briefly, a trimethylaryl stannane precursor was reacted with ^{18}F fluorine, ^{18}F-F2, by electrophilic aromatic substitution to provide the fluorinated compound with subsequent acidic hydrolysis by hydrobromide, HBr, resulting in ^{18}F-Fluoro-DOPA. All patients were pre-treated with Carbidopa 150-200 mg (Lodosyn 25 mg).

The CT protocol included a whole-body, contrast-enhanced (post-injection delay, 16 s and 65 s) series and was obtained following an intravenous injection of 120 ml of a tri-iodinated, non-ionic contrast medium (Iomeron 300; Bracco, Milan, Italy) at a rate of 4 ml/s, followed by a 50-ml saline flush. CT images of all series were reconstructed with a soft-tissue kernel (B30f) using the following CT acquisition parameters: tube voltage, 120 mAs; tube current, 230 kV; collimation, 64×0.6 mm; reconstruction orientation, transverse; reconstruction section thickness, 3 mm with 2-mm increments; matrix, 512×512. The CT data were acquired during suspended expiration. Without changing the patient's position, PET images were obtained approximately 20 min following the intravenous administration of 250 MBq 18F-DOPA. PET was performed over five to six bed positions for three min/bed position. PET images were reconstructed using the TrueX algorithm (Siemens, Erlangen, Germany) with four iterations per 21 subsets, a matrix size of 168×68 and a slice thickness of 5 mm. The attenuation correction was based on the CT maps. All CT and PET data were co-registered and fused, thus color-coded PET/CT images were generated. Maximum tissue standardized uptake values (SUV_{max}) were based on elliptic regions of interest manually drawn around lesions of ^{18}F-DOPA uptake.

Image interpretation. Physicians who were experienced in nuclear medicine and radiology interpreted the images of all patients. The readers were blinded to the identity and history of the patients, the specific indication (primary search, staging in metastatic history), the histological and radiological reports, as well as to the clinical history. In the first session, CT and PET images were reviewed independently, in random order. CT was evaluated on a Picture Archiving and Communication System (PACS) workstation, whereas PET images were evaluated using a Syngo Multi-Modality workstation using a "TrueD" software module (Siemens, Erlangen, Germany). On CT, a lesion was rated as a PARA if (i) the characteristic strong contrast enhancement was present or (ii) for non-enhancing lesions, the anatomic localization was typical and a secondary typical CT feature (necrosis or calcification) was present. On PET, a lesion was rated as a PARA if an increased DOPA uptake was present. After a time interval of six weeks, PET/CT images were evaluated in consensus in a different, randomized sequence taking into account the above-described PET and CT criteria. A lesion was rated as a PARA if (a) the PET was positive or (b) if the PET was negative, but the lesion showed a strong contrast enhancement (*i.e.*, the most characteristic CT feature). PET-negative lesions without strong contrast enhancement were not rated as a PARA, even if the anatomic localization and the secondary CT features (necrosis or calcification) were suggestive of a PARA.

For further analysis, imaging findings were compared to the overall final diagnosis. Final diagnosis was established by histological findings of surgically proven lesions. Notably, all patients who showed at least one suspicious lesion by PET/CT in routine practice were evaluated by histological workup. In patients with more than one suspected lesion, all were rated as PARA if one of these lesions was histologically proven to be a PARA. Such a strategy has been used in previous studies (17-20) because, in patients with multiple metastases, not every single metastasis can be verified histologically.

Final diagnosis was rated as positive if a detected lesion was (i) confirmed histologically as PARA and (ii) a lesion increased in size, activity or was of new onset in follow-up imaging (in case of a history of metastatic PARA). The final diagnosis was rated as negative if a detected lesion was (a) histologically proven not to be a PARA and (b) if there was no detected lesion, if previous clinical findings, including laboratory results, returned to normal values and/or the initial negative PET/CT scan was confirmed by follow-up imaging after at least one year. For further analysis, a lesion-based comparison was performed between all the patients in whom a lesion was detected by ^{18}F-DOPA PET/CT and by the stand-alone techniques CT and PET. Patients with a diffuse metastatic pattern, which was the case for more than 20 lesions, were not included because, in these cases, a sufficient correlation of our detected lesions was not possible.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA). Metric data, such as age, are presented using mean±standard deviation (SD), while nominal data are presented using absolute frequencies and percentages. Calculations were performed on a per-lesion basis, as well as patient-based. Sensitivity, specificity, positive predictive value (PPV) and accuracy were calculated for CT, PET and PET-

Table I. *The location of lesions and the final diagnoses.*

Patient no	Gender	Age	Initial diagnosis/relapse	Localization	Modality	Final diagnosis
1	f	25	ID	Glomus jugularis left	A, B, C	1
2	f	60	ID	Glomus caroticum bilateral	A, B, C	1
3	m	63	ID	Paraaortal-retroperitoneal right	A, B, C	1
4	f	63	ID	Glomus caroticum right	A, B, C	1
5	f	40	ID	Paraaortal-retroperitoneal right	A	0
6	f	73	R			0
7	f	27	ID			0
8	m	65	ID	Mediastinum - paravertebral right	A	0
9	f	35	R	bones (multiple)	A, B, C	1
10	m	62	ID			0
11	m	30	ID			0
12	m	71	ID			0
13	m	42	ID			0
14	f	29	ID	Glomus caroticum right	A, B, C	1
15	m	30	R	Pulmonal, retroperitoneal, mesenteric lesions	A, C	1
16	m	65	ID	Glomus caroticum left	A, C	1
17	f	29	R	Paraaortal-retroperitoneal right	C	1
18	m	39	ID	Glomus caroticum	A, B, C	1
19	m	50	ID			0
20	f	70	R	Bones (multiple), retroperitoneal - paraaortal right	A, B, C	1
21	m	64	ID			0
22	m	29	R	Bones (multiple), liver	A, B, C	1
23	m	32	ID			0
24	f	44	R	Bones (multiple), mediastinal lesions	A, B, C	1
25	f	42	R	Bones, liver	A, B, C	1
26	f	37	R	Lymph nodes, cervical right	B, C	1
27	f	19	R			0
28	f	63	ID			0

ID, Initial diagnosis; R, relapse; A, CT; B, PET; C, PET/CT; 1, positive final diagnosis; 0, negative final diagnosis.

CT. Histopathology was used as the gold standard. Significant differences in sensitivity and specificity were assessed using Cochran Q tests, as generalized estimating equations (GEE) did not work properly because some subgroups showed zero variances. Differences between diagnostic modalities were tested by the Cochran Q test. A p-value ≤0.05 was considered to indicate significant results.

Results

The location of lesions and the final diagnoses can be seen in Table I. In 15 of 28 patients (confirmed as PARA), there were lesions with a maximum diameter of 22.9±15.4 mm (range=7-63). These lesions showed a max_{suv} of 34.8±34.8 (range=5-115.1). In three patients with final positive results, ^{18}F-DOPA PET was negative, while in two patients with positive final CT results was negative.

Overall (including all modalities), 45 lesions were detected. On PET, 13 were negative and 32 positive (31 true positive, 11 false negative), on CT, 16 negative and 29 positive (27 true positive, 15 false negative). In the per-lesion analysis, there was a sensitivity of 64.3% for CT, 73.8% for PET and 100% for PET/CT with a PPV of 93.1% for CT, 96.9% for PET and 100% for PET/CT (Figure 1). When the body was divided into two regions, parasympathetic and sympathetic, the sensitivity for parasympathetic region was 88.9% for CT, 66.7% for PET and 100% for PET/CT and, for the sympathetic region, 57.6% for CT, 75.8% for PET and 100% for PET/CT. The PPV for parasympathetic region was 100% for CT, 85.7% for PET and 100% for PET/CT and, for the sympathetic region, 90.5% for CT, 100% for PET and 100% for PET/CT (Figure 1).

On a per-patient basis, the sensitivity, specificity and accuracy for CT was 86.7%, 84.6% and 85.7%, respectively and, for PET, 80%, 100% and 89.3%, respectively, and, for PET/CT, 100% (Figure 2). The hormonal status in our patients was not associated in all cases with the tracer uptake on the lesions (hormonal status-positive: PET in 5 cases positive, in 6 cases negative; hormonal status-negative: PET in 10 cases positive and in 6 cases negative).

In one patient (no. 26), a lymph node was detected in the cervical region. As this lesion was not the primary (relapse-metastasis), this finding was assigned to the sympathetic region.

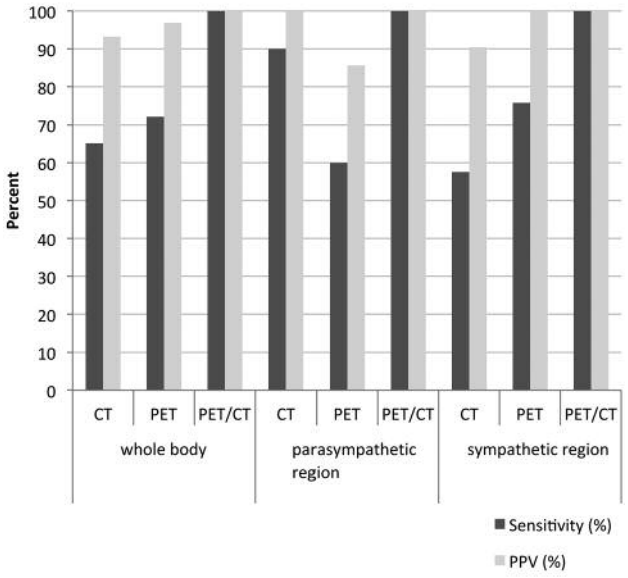

Figure 1. *Sensitivity and positive predictive value on CT, PET and PET/CT for the whole body is presented (further separations for the head and neck region, as well as for the sympathetic region -thorax, abdomen and pelvis- are shown). Pre-lesion-based analysis.*

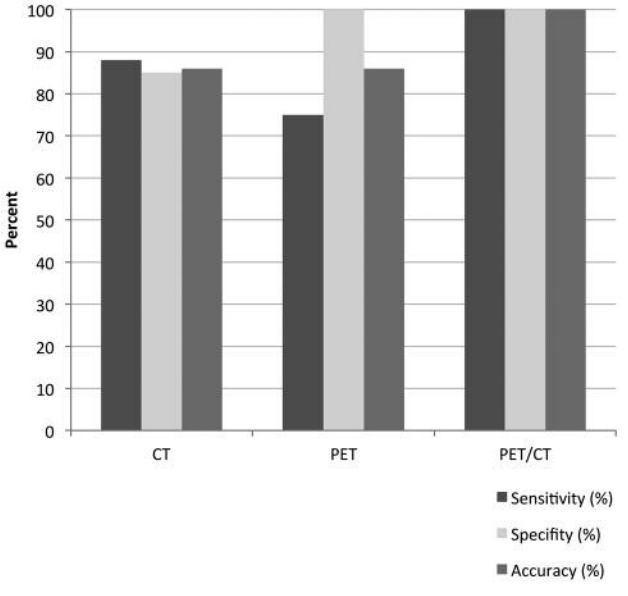

Figure 2. *Sensitivity, specificity and accuracy of CT, PET and PET/CT are shown on a per-patient-based analysis.*

On CT, in 15 patients, a PARA was suspected, whereas, in 13 of those, the diagnosis was confirmed as positive. In 2/15 patients, the CT diagnosis of a PARA was false-positive. In two patients, the CT diagnosis was false-negative. CT was false-positive in two cases, where the hormonal status was negative in both. CT was false-negative in two cases, while the hormonal status was positive (size of lesions: 7 mm, 14 mm).

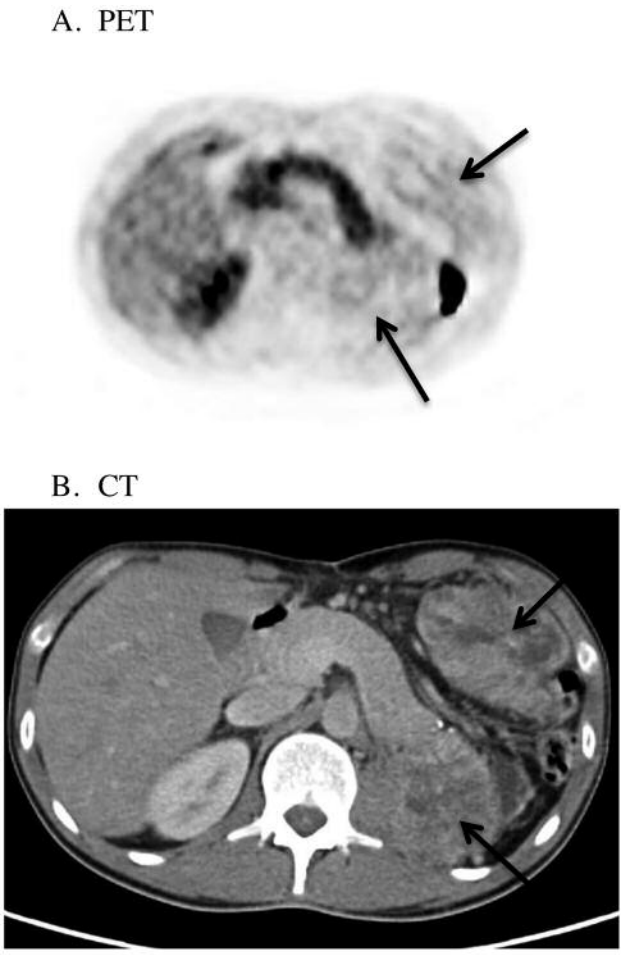

Figure 3. *Case of PET-negative metastatic paraganglioma, positive in CT.*

On PET, a PARA was suspected in 12 patients. In all of them, the diagnosis was confirmed positive. In three patients with a positive final diagnosis of a PARA, the PET was negative (Figure 3). The hormonal status was negative in two cases and positive in one (size only for one case available: 14 mm). On PET/CT, in 15 patients, diagnosis of a PARA was made and all of them were confirmed as positive. No false-positive or false-negative diagnosis was made.

When the body was divided into parasympathetic and sympathetic regions, CT suggested a positive diagnosis for a parasympathetic PARA in six patients and, for nine patients, in the sympathetic region. The two false-positive diagnoses, as well as the two false-negative results, were located in the sympathetic region. PET was positive in five patients with a PARA in the parasympathetic region and in

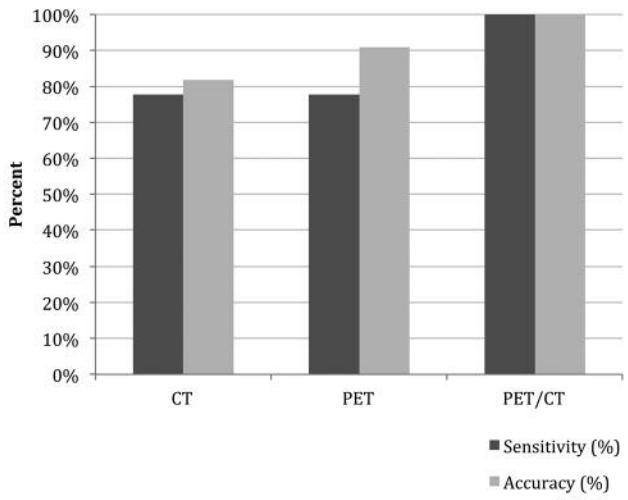

Figure 4. *Sensitivity and accuracy for CT, PET and PET/CT for the sympathetic region are presented. Per-patient-based analysis considering the sympathetic region (not the parasympathetic region).*

seven cases for the sympathetic region. The three false-negative results included one for the parasympathetic region and two for the sympathetic region. The 15 correct diagnoses in PET/CT comprised of six patients with a parasympathetic PARA and nine patients with a PARA in the sympathetic region. Sensitivity and diagnostic accuracy for the head and neck region alone were not calculated because of the low number of positive patients (six patients). Sensitivity in the sympathetic region for CT, PET and PET/CT were 78%, 78% and 100%, respectively, and, for accuracy, 82%, 91% and 100%, respectively (Figure 4). No significant differences could be detected between the imaging modalities (p=0.223).

Discussion

Early detection of PARA is crucial and has a major effect on treatment and prognosis, particularly in metastatic disease (21). The introduction of PET/CT into clinical practice offers advantages for detection of this tumor entity. CT provides accurate anatomical detail but with low specificity in distinguishing between tumors derived from the sympathetic nervous system and other tumor entities (22). Different functional imaging agents target PARA tumor cells through different mechanisms. ^{18}F-DOPA enters the cell *via* the amino acid transporter, based on the capability of PARA and other neuroendocrine tumors to take up decarboxylate and store amino acids and their biogenic amines and, in the case of ^{18}F-DOPA, reflect aromatic–amino-acid–decarboxylase activity (23, 24).

In a meta-analysis of the diagnostic performance of ^{18}F-DOPA in patients with PARA/pheochromocytomas, the pooled results indicated that ^{18}F-DOPA PET and PET/CT demonstrate high sensitivity (91%) and high specificity (95%) on a per patient-based analysis and good sensitivity (79%), as well as high specificity (95%) on a per lesion-based analysis, and that they are accurate methods for the diagnosis of PARA/ pheochromocytomas (7). A limitation of this analysis was the lack of the calculation of pooled sensitivity and specificity of ^{18}F-DOPA PET or PET/CT in different forms of PARA/ pheochromocytomas, for example, adrenal *vs*. extra-adrenal, sympathetic *vs*. parasympathetic, functioning *vs*. non-functioning, inherited *vs*. sporadic and metastatic *vs*. non-metastatic tumors. In fact, the frequent mixing of these forms of PARA/ pheochromocytomas in the patient population of the included studies hampered the data extraction and the separate calculation of the diagnostic performance of ^{18}F-DOPA PET in such groups (7).

In our study, we used ^{18}F-DOPA PET/contrast-enhanced CT in unselected patients with clinically suspected PARA. The tracer showed a moderate sensitivity (66%) for PARA in the head and neck region and is, therefore, clearly not suitable for their detection. In contrast to our results, other authors (25) found that 18F-DOPA PET seems to be the most sensitive imaging method for the detection of head and neck PARA, probably due to the high tracer avidity of these neoplasms and the favorable lesion-to-background ratio in the head and neck. Better results were found with CT and, with the use of ^{18}F-DOPA PET, CT sensitivity increased to 100%. Based on our results, CT is not suitable for the detection of PARA in the thorax/abdomen/pelvis due to its moderate per-lesion based sensitivity (58%). PET showed a better sensitivity and PET/CT an excellent sensitivity (100%).

In a per-patient analysis, CT seems to be superior compared to ^{18}F-DOPA PET (sensitivity: 87% *vs*. 80%). Although both CT and PET showed false-negative results, only CT showed false-positive results. Possible sources of 18F-DOPA PET false-negative results could be related to several factors, such as the small size of the lesion, the location of the tumor near organs with high physiological 18F-DOPA uptake (such as the pancreas, biliary and urinary systems) or loss of ^{18}F-DOPA uptake due to tumor dedifferentiation. Genetic factors may also affect the 18F-DOPA uptake in PARA in which there is a reported sensitivity of about 100% in succinate dehydrogenase complex subunit D *SDHD* but only about 40% in non-*SDHD*. Succinate dehydrogenase complex subunit B (*SDHB*) gene mutations may result in PARA for which ^{18}F-DOPA PET shows a lower sensitivity than for non-*SDHB*-related lesions (14). In this context, we have to mention that all our patients were pre-treated with carbidopa, which decreases the carboxylation and subsequent renal clearance of ^{18}F-DOPA to increase the tumor-to-background ratio of tracer uptake (7). The very high (100%) specificity of ^{18}F-DOPA PET in our patients, in whole body, is in

accordance with the reports of other authors (7). The hormonal status of our patients did not show a correlation in all cases with enhanced tracer-uptake.

The hybrid diagnostic modality, ^{18}F-DOPA PET/CT, showed a 100% sensitivity and positive predictive value on a per-lesion-based analysis (whole body, parasympathetic region and thorax/abdomen/pelvis region). However, a contrast-enhanced CT should be obtained to achieve the maximum diagnostic performance. A 100% sensitivity, specificity and accuracy were found on a per-patient-based analysis. Therefore, ^{18}F-DOPA PET/CT is an excellent and accurate diagnostic tool for the imaging of sympathetic and parasympathetic PARA.

In a recent study, ^{18}F-DOPA PET was compared with ^{68}Ga-DOTA-Tyr3-octreotide (^{68}Ga-DOTA-TOC) PET for the diagnosis and staging of carbidopa-untreated patients with PARA. The authors concluded that ^{68}Ga-DOTA-TOC PET may be superior to ^{18}F-DOPA PET and diagnostic CT in providing valuable information for pre-therapeutic staging of extra-adrenal paraganglioma particularly in surgically inoperable tumors and metastatic or multifocal disease (12). The commercially unavailable 6-[^{18}F]fluorodopamine (FDA) shows, in only one study, the best results in a head-to-head comparison with other commercially available tracers, such as ^{123}I-MIBG, ^{18}F-FDG and ^{18}F-DOPA (18). Yet, the radiopharmaceutical preparation of F18 Dopamine is cumbersome and yields only a small amount of tracer for injection, resulting in low count studies. With MIBG, drug interference has to be avoided, which is of minor concern in studies using ^{18}F-DOPA. The well-known ^{18}F-FDG could be used in *SDHB* mutation carriers (14) and the ^{123}I-MIBG is a good alternative if a PET camera is not available. In a recent meta-analysis, there was only a small additive value for CT and MRI functional imaging, although no hybrid imaging methods were considered (13).

In our study, we chose strong criteria for the image interpretation of ^{18}F-DOPA PET, CT and ^{18}F-DOPA PET/CT. We found that ^{18}F-DOPA PET/CT was an excellent first-line diagnostic modality -superior to PET and CT- for the detection of PARAs in our patients. Unlike ^{18}F-DOPA, ^{68}Ga-DOTA-TOC provides valuable information about tumor cell receptor status for planning peptide receptor radionuclide therapy, which is particularly useful in patients with surgically inoperable tumors or metastatic disease (26-30). Prospective studies are warranted to determine the true clinical value of ^{68}Ga-DOTA peptide PET/CT compared to ^{18}F-DOPA PET/CT.

Conclusion

Our study demonstrated that ^{18}F-DOPA PET/contrast-enhanced CT is an excellent "one-stop diagnostic modality" for the assessment of unselected patients with clinically suspected PARA.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

This study was approved by the local Ethics Committee and, for this retrospective type of work, informed consent of patients was not required.

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