Tracer development for detection and characterization of neuroendocrine tumors with PET

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Chapter 4
Staging of carcinoid tumours with ^{18}F-DOPA PET: a prospective, diagnostic accuracy study

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Summary

Background

To assess individual treatment options for patients with carcinoid tumours, accurate knowledge of tumour localisation is essential. We aimed to test the diagnostic sensitivity of 6-[fluoride-18]fluoro-levodopa (^{18}F-DOPA PET), compared with conventional imaging methods, in patients with carcinoid tumours.

Methods

In a prospective, single-centre, diagnostic accuracy study, ^{18}F-DOPA PET with carbidopa pretreatment was compared with somatostatin-receptor scintigraphy (SRS), CT, and combined SRS and CT in 53 patients with a metastatic carcinoid tumour. The performance of all imaging methods was analysed for individual patients, for eight body regions, and for the detection of individual lesions. PET and CT images were fused to improve localisation. To produce a composite reference standard, we used cytological and histological findings; all imaging tests, including secondary assessments for newly found lesions; follow-up; and biochemical data. Sensitivities were calculated and compared.

Findings

In patient-based analysis, we recorded sensitivities of 100% (95% CI 93–100) for ^{18}F-DOPA-PET, 92% (82–98) for SRS, 87% (75–95) for CT, and 96% (87–100) for combined SRS and CT (p=0.45 for ^{18}F-DOPA PET *vs* combined SRS and CT). However, ^{18}F-DOPA PET detected more lesions, more positive regions, and more lesions per region than combined SRS and CT. In region-based analysis, sensitivity of ^{18}F-DOPA PET was 95% (90–98) versus 66% (57–74) for SRS, 57% (48–66) for CT, and 79% (70–86) for combined SRS and CT (p=0.0001, PET *vs* combined SRS and CT). In individual-lesion analysis, corresponding sensitivities were 96% (95–98), 46% (43–50), 54% (51–58), and 65% (62–69; p<0.0001 for PET *vs* combined SRS and CT).

Interpretation

If the improved tumour localisation seen with ^{18}F-DOPA-PET compared with conventional imaging is confirmed in future studies, this imaging method could replace use of SRS, help improve prediction of prognosis, and be used to assess patients' response to treatment for carcinoid tumours.

Introduction

Neuroendocrine tumours are a heterogeneous group of slow-growing lesions arising from neuroendocrine cells, of which carcinoid tumours are the most common. These tumours are often located in the abdomen and can produce and secrete a large variety of products because of their intrinsic ability to take up, accumulate, and decarboxylate amine precursors[1]. In metastatic disease, these products, such as serotonin and catecholamines, can bypass the first-pass metabolisation and inactivation by the liver and can cause symptoms. Treatment options for carcinoid tumours include curative or debulking surgery, medical treatment with somatostatin analogues, and interferon[2].

To assess individual treatment options, accurate knowledge of tumour localisation, biochemical activity, and progression is essential. The initial work-up for patients with

carcinoid tumours consists of morphological imaging methods such as CT, combined with functional whole-body imaging with somatostatin-receptor scintigraphy (SRS)[3,4,5]. However, CT and MRI of the abdomen have difficulties in correctly separating tumours and mesenterial metastases from intestinal structures[6,7,8]. Furthermore, SRS can produce false-negative findings, because of the variable affinity and expression of somatostatin receptors and the restricted resolution of gamma cameras and single-photon-emission tomography (SPECT) methods[9,10].

PET using the catecholamine precursor 6-[fluoride-18]fluoro-levodopa (^{18}F-DOPA) has emerged as a new imaging method for neuroendocrine tumours[6]. By contrast with other methods, this procedure is based on the intrinsic property of neuroendocrine tumours to take up amine precursors, such as ^{18}F-DOPA[11,12,13,14,15]. The combination of this specific tracer with the high resolution provided by PET could lead to a clinically relevant improvement in the detection and staging of neuroendocrine tumours. A few small studies[6,16,17] have shown some potential of ^{18}F-DOPA PET in small and heterogeneous groups of patients with neuroendocrine tumours.

Therefore, the aim of this study was to compare the diagnostic sensitivity of ^{18}F-DOPA PET with that of conventional imaging methods such as SRS and CT, in a large and homogeneous population of patients with carcinoid tumours.

Methods

Patients

Eligible patients for this prospective single-centre diagnostic accuracy study included: those who were newly referred to our centre (which serves the northern region of the Netherlands) with a carcinoid tumour, based on clinical or biochemical findings, and at least one abnormal lesion detected on CT, MRI, sonography, or SRS; and those known to have a histopathologically proven carcinoid tumour, who had a clinical indication for restaging, and who had at least one abnormal lesion on conventional imaging studies. We excluded patients younger than 18 years, those who were pregnant, and those in whom an additional non-carcinoid tumour had been diagnosed. Every consecutive patient underwent ^{18}F-DOPA PET, SRS, and CT scanning of the abdomen and (if needed) of the chest, and biochemical analysis. Imaging methods were undertaken in a random order. The local medical ethics committee approved the study and all patients gave written informed consent.

Procedures

^{18}F-DOPA was produced in the radiochemical laboratory of our hospital as described previously[18]. Patients fasted for 6 h before the examination and were allowed to continue all medication. Whole-body two-dimensional PET images were acquired 60 min after intravenous use of ^{18}F-DOPA (130–230 MBq, radiation dose 2.6–4.6 mSv)[19], on a Siemens ECAT HR+ (high-resolution) positron camera (Siemens, Knoxville, TN, USA) with attenuation correction (7–10 bedpositions of 5 min emission and 3 min transmission scan). For the reduction of tracer decarboxylation and subsequent renal clearance, all patients received 2 mg/kg carbidopa orally as pre-treatment, 1 h before the ^{18}F-DOPA injection, to increase tracer uptake in tumour cells[19,20,21].

Two nuclear medicine physicians (KPK, PLJ), who were masked to the results of other imaging examinations and to the extension of tumour spread in study patients, interpreted the ^{18}F-DOPA PET images independently. Only lesions in every body region that clearly showed more activity than that seen in patients and regions not known to contain tumours were regarded as abnormal. If discrepancies were found, a consensus reading was done. Since ^{18}F-DOPA PET is a new test, these physicians built expertise in the first 20 cases, and then reviewed these early cases again in the second half of 2004.

According to Dutch standards, we obtained planar total-body and SPECT images 24 h after intravenous administration of 200 MBq indium-111-octreotide (Octreoscan; Mallinckrodt, Petten, Netherlands; radiation dose 10 mSv)[22], using standard methods (Siemens Multispect 2 gamma camera, medium-energy collimator, 10 min spotviews, 64 projections of 30 s). If interfering bowel activity was seen, images were recorded again at 48 h[23]. We withheld laxatives only if patients presented with diarrhoea. All patients were allowed to continue their treatment.

SRS scans were interpreted by dedicated specialists as part of routine care and independently reread by a nuclear medicine physician (PLJ), who was masked to the results of other imaging examinations and to the extension of tumour spread in the study patients.

CT (4–16 slice, Siemens Somatom Sensation, Siemens Medical Systems, Erlangen, Germany; radiation dose 8–20 mSv)[24] was done with oral contrast and intravenous contrast enhancement (Visipaque 270, 120 ml, 2.5 ml/s). The reconstruction interval was 3–8 mm. All patients underwent CT of the entire abdomen and pelvis. The CT imaging area was extended to include the chest in 26 patients, and the neck and chest in three patients because of clinical suspicion of tumours in those regions.

CT scans were interpreted by dedicated specialists as part of routine care. At the time of image fusion, results were reviewed again by the investigators, and for discrepancies, consensus was reached after multidisciplinary discussion.

As a composite reference standard for the presence of tumour lesions, we used all available cytological, histological, follow-up, and imaging findings, because cytological or histological verification of every lesion is not feasible and not justifiable ethically in all patients because of the tumour load in many of these patients. If possible, new findings on PET were verified by other investigations other than CT and PET–CT fusion. These were: MRI (n=8), bone scintigraphy (n=9), planar radiographs (n=13), sonography (n=4), surgery (n=10), or biopsy (n=5). These investigations included verification of lesions in body regions that were outside the CT field. However, in many cases, the number of new and previously unknown lesions on PET imaging was high, which led to the analysis of every individual localisation.

After images had been interpreted, CT and ^{18}F-DOPA PET images were fused automatically by use of three-dimensional fusion software (Siemens Leonardo workstation) with manual fine adjustments. Experienced physicians compared the fusion images with the results of visual matching for the accuracy of lesion localisation.

As markers for serotonin metabolism, we measured serotonin concentrations in platelets and urinary 5-hydroxyindole acetic acid (5-HIAA) in a 24-h urine sample (upper reference limits 5.4 nmol/10^9 platelets and 3.8 mmol/mol creatinine, respectively). As markers of catecholamine metabolism, we measured urinary concentrations of metanephrine, normetanephrine, and 3-methoxytyramine in a 24-h urine collection (upper reference limits

99, 260, and 197 μmol/mol creatinine, respectively)[14,25]. Sampling procedures and analytical methods were done as previously described[24,25,26,27,28,29,30]. We measured serum concentrations of chromogranin A by use of a radioimmunoassay (Cga-React, Cis Bio International, Marcoule, France) as a marker for tumour volume (reference interval 20.0–100.0 mg/L).

Statistical analysis

Analysis was done at three levels. At the first level, individual patients were analysed. Image studies were regarded as positive if a patient had at least one lesion. The second level of analysis addressed body regions—head and neck, mediastinum, lungs, liver, abdomen and pelvis, bone, and soft tissue of the extremities. A region was regarded as positive, if at least one lesion was detected in that region. The third level analysed the individual lesions that were counted for all imaging methods. If the number of lesions in one region (e.g., liver) was more than ten, the number of lesions was truncated at ten lesions for that region to avoid bias.

SRS is a whole-body procedure, whereas CT covers only the most relevant parts of the body. To eliminate possible bias towards whole-body imaging methods, we only analysed regions for which all three imaging methods were available.

Sensitivities were calculated with the composite reference standard and were compared with paired observations and McNemar's test. Patient-based sensitivity was calculated as the proportion of patients with at least one lesion detected. Regional sensitivity was calculated by dividing the number of patients with a positive region (detected with that particular method) by the total number of patients in whom that region was positive by any imaging method. We calculated lesion-based sensitivity by dividing the number of lesions detected with a particular method by the total number of lesions detected by any method. Pitman's test for paired data was used to compare the number of lesions per region. Wilcoxon's test was used to compare the number of patients with five or fewer positive body regions detected by PET and by combined SRS and CT. For correlations, Spearman's *r* test was calculated. Significance level was 0.05, two-sided. We did statistical analysis by using the SPSS package version 12.0.

Results

Between October, 2003, and February, 2006, we asked 68 consecutive patients to participate in the study (figure 1); however, three declined PET scanning, and we could not obtain all required information for 12, because of various logistical reasons (e.g., no biochemistry or pathology findings, no SRS). Sensitivity was calculated in the remaining 53 patients assessed, of whom 25 were newly diagnosed with carcinoid disease (table 1). The median time between PET and CT was 59 days (range 1–191) and between PET and SRS was 47 days (1–206). Mean values for these intervals were 25 days (SD 57) and 42 days (75), respectively. In retrospect, the interval was short compared with disease progression in all patients. One patient developed a carcinoid crisis after intravenous administration of ^{18}F-DOPA, which was treated successfully[31].

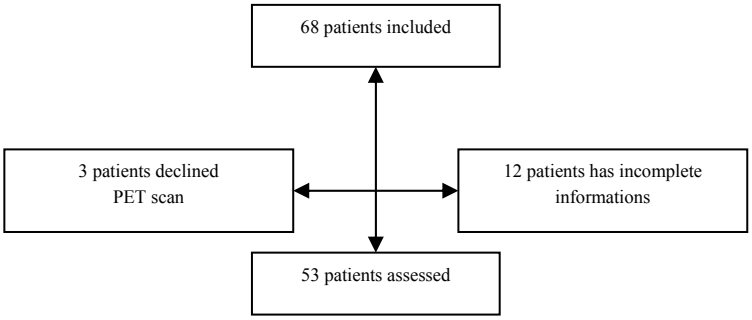

Figure 1. Study flowchart of patient

Table 1. Patients' characteristics (n=53)

	Value
Sex (male/female)	25/28
Age (years)	59 (35-77)
Newly diagnosed patients vs. known disease	25/28
Histological vs. biochemical diagnosis	52/1
Primary localisation	
Lung	5
Duodenum	3
Jejunum	3
Ileum	25
Colon	1
Unknown	16
Carcinoid syndrome	21
Treatment during scan	
Somatostatin analogues only	15
Somatostatin analogues and interferon	1
Biochemical variables	
Platelet serotonin >5.4 nmol/10^9 platelets	42/51
Urinary 5-HIAA >3.8 mmol/mol creatinine	35/51
Urinary metanephrine >9.9 µmol/mol creatinine	5/48
Urinary normetanephrine >260 µmol/mol creatinine	7/48
Urinary 3-methoxytyramine >197 µmol/mol creatinine	16/48
Serum chromogranin A >100 mg/L	21/31

Data are number of patients or median (range).

^{18}F-DOPA PET produced high-quality tomographical images that were easily interpretable (figure 2). More patients had positive lesions detected by ^{18}F-DOPA PET than by SRS or by combined SRS and CT (table 2; ^{18}F-DOPA PET vs combined SRS and CT, p=0.45). Four patients were recorded as negative on SRS, seven on CT, and two on combined SRS and CT (both of whom were shown to have tumours when assessed 6 months later with SRS).

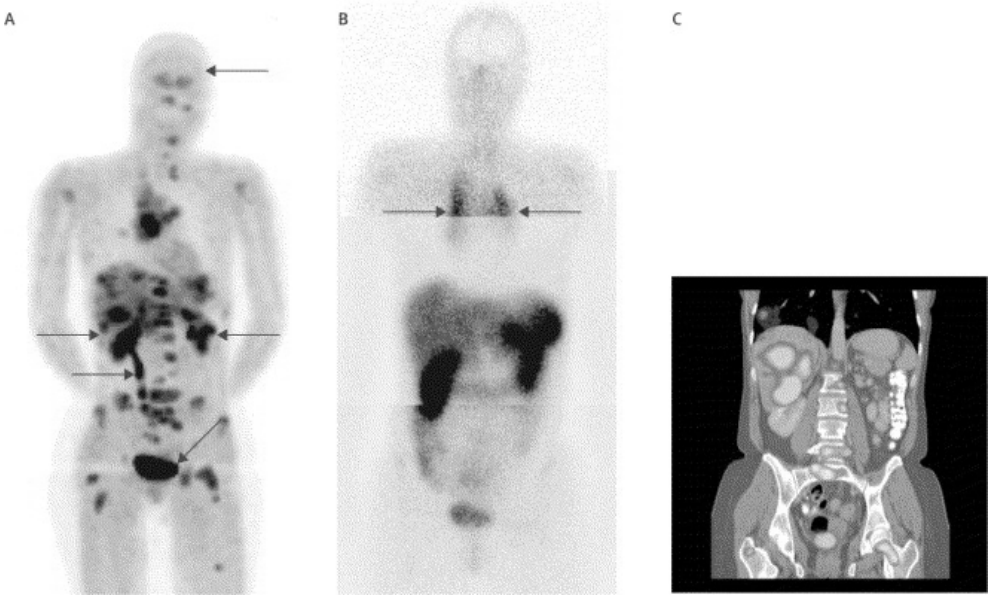

Figure 2. Full-color in appendix. Imaging of a patient with carcinoid disease and metastases in the bone, mediastinum, liver, and abdomen. (A) ^{18}F-DOPA PET imaging. Red arrows indicate areas with physiological ^{18}F-DOPA uptake (striatum, kidneys, ureter, bladder), whereas all other black spots are tumour lesions. (B) Planar SRS imaging. Arrows indicate mediastinal tumour lesions. (C) CT–PET fusion imaging. Coloured areas indicate tumour lesions. In this patient, both planar and SPECT SRS missed most lesions found with ^{18}F-DOPA PET imaging. Abdominal and femoral lesions were not recorded on CT.

Table 2. Patient-based analysis

	Positive lesions (n)	**Sensitivity (95% CI)**	**Lesions detected Per patient (median [range])**
^{18}F-DOPA PET	53	100% (93-100)	12 (1-36)
SRS only	49	92% (82-98)	4 (0-20)
CT only	46	87% (75-95)	6 (0-20)
SRS and CT	51	96% (87-100)	10 (1-36)

Table 3 shows region-based and lesion-based sensitivities. Of 326 regions that were assessable, 122 (37%) were judged as positive for tumour. ^{18}F-DOPA PET detected 117 of these positive regions (sensitivity 95%), whereas SRS only detected 80 (sensitivity 66%; table 3). When data from SRS and CT were combined, sensitivity reached 79% but was substantially lower than that for ^{18}F-DOPA PET (^{18}F-DOPA PET *vs* combined SRS and CT, p=0.0001).

Table 3. Sensitivity of imaging methods in patients with carcinoid tumours

	^{18}F-DOPA PET (95% CI)	**SRS (95% CI)**	**CT (95% CI)**	**SRS and CT (95% CI)**	**Positive regions or lesions (n)**
Region-based analysis					
Mediastinal*	92% (74-99)	69% (38-91)	15% (1-46)	69% (38-91)	13
Lung*	60% (13-96)	80% (27-99)	40% (40-87)	80% (27-99)	5
Liver	98% (88-100)	77% (62-89)	75% (60-87)	89% (75-96)	44
Pancreas	100% (26-100)	0% (0-74)	67% (7-100)	67% (7-100)	3
Abdomen or pelvis	97% (86-100)	72% (55-85)	62% (44-77)	87% (72-96)	39
Bone	92% (63-100)	31% (1-62)	46% (19-75)	54% (25-81)	13
Extremities	100% (45-100)	20% (0-73)	20% (0-73)	20% (0-73)	5
Total	95% (90-98)†	66% (57-74)	57% (48-66)	79% (70-86)	122
Lesion-based analysis					
Mediastinal*	95% (82-100)	41% (25-58)	8% (1-21)	44% (28-60)	39
Lung*	55% (23-84)	53% (16-77)	36% (10-70)	64% (30-90)	11
Liver	97% (95-94)‡	53% (48-59)	66% (61-71)	73% (68-78)	360
Pancreas	100% (26-100)	0% (0-74)	67% (7-100)	67% (7-100)	3
Abdomen or pelvis	96% (93-98)‡	41% (35-48)	49% (42-56)	64% (57-71)	208
Bone	97% (88-100)	31% (20-44)	41% (29-54)	48% (35-61)	61
Extremities	100% (45-100)	20% (0-73)	20% (0-73)	20% (0-73)	5
Total	96% (95-98)‡	46% (43-50)	54% (51-58)	65% (62-69)	687

No lesions were found in the head and neck region.
* Only regions in field of view of all imaging procedures compared.
† ^{18}F-DOPA PET *vs* combined SRS and CT, p=0·0001.
‡ ^{18}F-DOPA PET *vs* combined SRS and CT, p<0·0001.

687 lesions were regarded as positive for tumour (table 3). ^{18}F-DOPA PET detected 658 lesions (sensitivity 96%), and SRS detected 315 (sensitivity 46%). Combined SRS and CT detected 450 lesions (sensitivity 65%; ^{18}F-DOPA PET *vs* combined SRS and CT, p<0.0001). Most positive lesions were found in the liver and abdomino-pelvic regions. ^{18}F-DOPA PET showed more lesions in these two regions than did combined SRS and CT (liver, 348 *vs* 261, p<0.0001; abdomen/pelvis, 203 *vs* 135, p<0.0001, respectively).
^{18}F-DOPA PET detected a mean of 2.2 (SD 0.93) positive regions per patient, versus 1.8 (0.81) detected by combined SRS and CT (p=0.0007). Based on our reference standard and follow-up, we could not record any false-positive lesions. The median number of lesions per patient was 12 for ^{18}F-DOPA PET and ten for combined SRS and CT (table 2). A mean of 13·5 lesions (SD 7.9) per patient were found overall (^{18}F-DOPA PET, 12.4 [7.4]; SRS, 6.2 [5.6]; combined SRS and CT, 8.8 [6.4]; ^{18}F-DOPA PET *vs* combined SRS and CT, p<0.0001). Thus, ^{18}F-DOPA PET detects an additional tumour-positive region in one of three patients, and detects four additional lesions per patient.

Urinary 5-HIAA excretion correlated with the number of tumour lesions detected by ^{18}F-DOPA PET (r=0.41, p=0.003), by CT (r=0.40, p=0.003), and by combined SRS and CT (r=0.38, p=0.006). Platelet serotonin concentrations correlated only with the number of tumour lesions detected by ^{18}F-DOPA PET (r=0.45, p=0.001). We recorded no correlation between the total number of tumours detected by any imaging method and concentrations of serum chromogranin A, urinary metanephrine, normetanephrine, or 3-methoxytyramine.

Discussion

We showed improved diagnostic sensitivity of ^{18}F-DOPA PET in staging and identification of carcinoid tumours, compared with currently applied, standard whole-body imaging with SRS. Compared with the combination of SRS with CT, ^{18}F-DOPA PET detected substantially more individual tumour lesions, more affected body regions, and more lesions per region. The improved lesion detection of carcinoid tumours with ^{18}F-DOPA PET provides a better understanding of the true extent of tumour spread in patients.

The precise mechanisms that determine the uptake of ^{18}F-DOPA in neuroendocrine tissues are not yet fully elucidated. The increased demand for amino acids, precursors in the overactive secretory pathways in neuroendocrine tumours[14], probably induces high uptake of this amino acid tracer in tumours by upregulation of transmembrane amino acid transporters. However, intracellular mechanisms, such as the highly active amino acid decarboxylase enzyme that is specifically active in neuroendocrine tumours, probably contribute to tracer uptake[11,13]. Overactivity of the catecholamine pathway could induce uptake of the catecholamine precursor tracer ^{18}F-DOPA, but ^{18}F-DOPA uptake was also present in the absence of increased urinary catecholamine metabolite secretion.

Only two small studies[6,17] have been reported on ^{18}F-DOPA PET scanning in patients with carcinoid tumours. Hoegerle and colleagues[6] did a lesion-based analysis (n=17) and found that ^{18}F-DOPA PET was more sensitive than SRS, CT, and MRI in detecting primary tumours and lymph-node metastases[6]. However, the performance of ^{18}F-DOPA PET for the detection of organ metastases was similar to that of SRS and worse than that of CT and MRI combined. Our improved results might be due to the use of oral carbidopa pretreatment, which increases the concentration and availability of ^{18}F-DOPA, thereby improving lesion detectability[32]. Hoegerle and co-workers[6] also used either CT or MRI, and studied fewer patients than we did. Becherer and colleagues[17] studied 23 patients, in whom 18 carcinoid tumours had been detected. ^{18}F-DOPA PET yielded high sensitivities in a region-based analysis similar to that used in our study. However, they detected fewer lesions in the lung (one of five patients who had lung tumours) than that seen in our study (three of five patients with lung tumours), although the numbers for this region were low in both studies. In the Becherer study[17], CT was the gold standard, and only lesions visible on ^{18}F-DOPA PET were regarded as false-positive.

A notable alternative for the imaging of neuroendocrine tumours is the use of a direct precursor for the serotonin pathway, ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP). This tracer has been investigated in 42 patients with various neuroendocrine tumours, after pretreatment with carbidopa[33]. ^{11}C-5-HTP PET detected carcinoid tumours in 13 of these patients, which was similar to our results with ^{18}F-DOPA. General applicability was limited by the difficult tracer synthesis of ^{11}C-5-HTP and the short half-life of an ^{11}C-based tracer of 20 min (half-life of an ^{18}F-based tracer is 110 min). Other developments include the search for new

radiolabeled somatostatin analogues for improved SRS SPECT imaging and SRS PET imaging[34,35,36].

A perfect gold standard is difficult to establish in any diagnostic accuracy study. In our study, new diagnostic methods might have been much better than current standard methods and might detect many unknown lesions that can never all be verified by cytological or histological analysis. Where possible, new findings were verified but we also assumed that when several lesions were verified by one technique, other lesions with identical and unequivocal uptake of this same tracer in the same patient could also be regarded as true tumours. The composite reference standard depended to some extent on the ^{18}F-DOPA PET results, and also on the CT and SRS results. Thus, our sensitivity values should be interpreted with caution.

In view of the many new lesions detected by ^{18}F-DOPA PET and the fact that cytological and histological verification has a risk of bleeding complications in these highly vascularised lesions, we did not consider the undertaking of ten biopsies in one patient as feasible.

Enhanced detection of lesions with ^{18}F-DOPA PET can lead to improvements in patients' care. In particular, the imaging method's excellent detection properties for liver, bone, and abdominal lesions could lead to alterations in surgery, medical treatment, and radiotherapy plans. Neuroendocrine tumours are currently classified by the WHO framework, which is based on morphological, clinical, and functional aspects of the tumour and its metastases. Treatment options depend on the tumour mass, functional activity, and growth behaviour of these tumours[37,38]. ^{18}F-DOPA PET could add important information on tumour localisations and prognosis and be used to aid research in the response to new molecular-targeted drugs, possibly even replacing SRS. However, we did not aim to record how use of this technique could change management, since we included patients with at least one histologically confirmed lesion or with known extensive disease. Furthermore, image interpreters need to develop experience with the technique before being completely accurate. With the excellent sensitivity of ^{18}F-DOPA PET recorded in patients with proven tumours, future studies are under way to measure the technique's detection capability in patients suspected of having a neuroendocrine tumour.

In summary, ^{18}F-DOPA PET significantly improves the detection of carcinoid tumours and their metastases compared with conventional techniques, and detects an additional tumour-positive region in one of three patients, and a mean of four additional lesions per patient. This technique might also contribute greatly to the staging of these patients. With the rapidly expanding availability of PET and increasing commercial production and distribution of radiotracers, the availability of tracers such as ^{18}F-DOPA will probably also increase. Furthermore, treatment of these patients is often centralised in well-equipped hospitals. Although ^{18}F-DOPA PET is almost sufficient for staging, addition of CT improves the localisation of lesions, which is relevant to guide surgical and radiotherapeutical procedures. The new trend of combined PET–CT scanning could therefore become a one-stop procedure in the staging of carcinoid tumours.

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