



Early ^{18}F -FDOPA PET/CT imaging after carbidopa premedication as a valuable diagnostic option in patients with insulinoma

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Abstract

Purpose Data on the diagnostic value of ^{18}F -FDOPA PET/CT in patients with insulinoma are limited and are focused on small patient populations explored using different PET/CT protocols and the inconsistent use of carbidopa premedication. The aim of this study was to improve the current knowledge about the diagnostic value of ^{18}F -FDOPA PET/CT combined with oral carbidopa premedication and early pancreatic imaging for tumour localization in patients with insulinoma-related hyperinsulinaemic hypoglycaemia (HH). The relationships among ^{18}F -FDOPA quantitative uptake parameters, insulin secretion and tumour pathological features were also investigated.

Methods Of 34 patients with suspicion of insulinoma-related HH examined by dual time-point carbidopa-assisted ^{18}F -FDOPA PET/CT, 24 with histologically proven insulinoma were retrospectively included. One patient underwent two PET/CT examinations for relapsing insulinoma after surgical excision. Thus, 25 preoperative ^{18}F -FDOPA PET/CT studies were finally retained and analysed. All studies were performed under carbidopa premedication (200 mg orally, 1–2 h prior to tracer injection). The PET/CT acquisition protocol included an early acquisition (5 min after ^{18}F -FDOPA injection) over the upper abdomen and a delayed whole-body acquisition starting 20–30 min later. The cytological and/or histopathological diagnosis of insulinoma was the diagnostic standard of truth.

Results ^{18}F -FDOPA PET/CT localized insulinoma in 21 of the 25 studies, leading to a primary lesion detection rate of 84%. Four lesions (19%) were detected only on early acquisitions. The false-negative tumour detection rates were, respectively, 22% and 12.5% in patients receiving and not receiving treatment for hypoglycaemic symptoms at the time of PET/CT. In benign insulinomas, the early maximum standardized uptake value (SUVmax) was significantly higher than the delayed SUVmax. Compared to the 21 benign lesions, four malignant insulinomas showed significantly higher ^{18}F -FDOPA uptake. Lesion size, fasting-end insulin and C-peptide levels correlated with tumour ^{18}F -FDOPA uptake, dopaminergic tumour volume and metabolic burden.

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Conclusion The present study showed that ^{18}F -FDOPA PET/CT combined with carbidopa premedication and early pancreatic acquisitions is a valuable diagnostic option in patients with insulinoma when GLP1R-based imaging is not available. The results also provide new insights into the relationships between tumour secretion and imaging phenotype in insulinomas.

Keywords ^{18}F -FDOPA · PET · Insulinoma · Hyperinsulinism · Carbidopa · Neuroendocrine tumours

Introduction

Insulinoma is an islet beta cell tumour that can cause life-threatening and debilitating hypoglycaemia. Insulinoma is diagnosed biochemically by prolonged fasting. Once insulinoma has been diagnosed, detection of the tumour is essential to permit curative surgical treatment and total resolution of preoperative symptoms [1–5]. A diagnostic imaging algorithm has recently been proposed for the detection of insulinomas, for the selection of malignant forms for peptide receptor radionuclide therapy, and to distinguish insulinoma from nesidioblastosis and postgastric bypass hypoglycaemia [6]. Accordingly, conventional imaging with CT and MRI should be considered as the first-line diagnostic imaging approach in patients with endogenous hyperinsulinaemic hypoglycaemia (HH). Molecular (nuclear) imaging usually complements morphological imaging and may rely on various radiopharmaceuticals. When available, radiolabelled glucagon-like peptide-1 (GLP-1) analogues are the first choice from among the available functional imaging tracers for PET/CT imaging [7]. PET/CT with ^{68}Ga -DOTA somatostatin analogues (SSAs) or carbidopa-assisted ^{18}F -FDOPA are advocated if ^{68}Ga -exendin-4 PET/CT is not available [8, 9].

No definitive evidence exists as to whether ^{18}F -FDOPA or ^{68}Ga -DOTA peptide PET/CT should be preferred, and prospective dedicated studies are needed.

The positive impact of ^{18}F -FDOPA PET/CT combined with oral carbidopa premedication and early pancreatic imaging has been demonstrated in clinical investigations involving adult patients with insulinoma-related HH [10, 11] and in preclinical studies [12]. Once internalized, ^{18}F -FDOPA is decarboxylated to ^{18}F -dopamine by aromatic amino acid decarboxylase (AADC) which accumulates in secretory vesicles [13]. Carbidopa is an efficient inhibitor of AADC and is able to drastically reduce physiological pancreatic uptake, increasing tumour detectability [10, 11]. However, a potential lowering of tumour uptake intensity has been suggested to occur after carbidopa premedication increasing the risk of false-negative PET/CT results [14, 15]. Thus, no final consensus has been reached about carbidopa premedication before ^{18}F -FDOPA PET/CT in patients with HH [16, 17].

Clinical data concerning the diagnostic value of ^{18}F -FDOPA PET/CT in patients with insulinoma are still limited and are mainly focused on small populations of patients explored using different PET/CT acquisition protocols with the

inconsistent use of carbidopa premedication. Thus, the primary aim of the present study was to improve the current knowledge about the diagnostic value of ^{18}F -FDOPA PET/CT combined with oral carbidopa premedication and early pancreatic imaging for tumour localization in patients with HH and histological proof of insulinoma. The relationships among quantitative ^{18}F -FDOPA uptake parameters, insulin secretion, and tumour pathological features were also investigated.

Materials and methods

Patient population

Data from all patients older than 18 years referred for clinical and biological suspicion of insulinoma-related HH to three academic NET centres in France (Strasbourg, Marseille and Nancy university hospitals) between January 2011 and July 2018 and who underwent ^{18}F -FDOPA PET/CT with carbidopa premedication and early imaging were retrospectively collected and analysed. Among these patients, only those with a final diagnosis of insulinoma-related HH according to biological criteria (i.e. positive fasting test) and/or pathological proof of pancreatic insulinoma were selected. Patients with spontaneous normalization of clinical symptomatology and/or biological investigations during follow-up were not included. Patients with pathological findings of synchronous insulinomas and nonfunctioning pancreatic neuroendocrine tumours were also excluded from the analysis.

The patient data collected included: (a) clinical symptomatology, (b) measurements of serum glucose, insulin and C-peptide concentrations during a supervised fasting test, (c) preoperative conventional imaging including at least abdominal contrast-enhanced CT or MRI performed less than 3 months before/after PET/CT, (d) preoperative echoendoscopic ultrasonography (EUS) when available, (e) pharmacological treatment (if any) of symptomatic hypoglycaemia at the time of PET/CT, and (f) tumour grade according the Ki-67 proliferation index. Clinical and biological follow-up of at least 3 months was obtained after pancreatic surgery. Resolution of preoperative clinical symptoms and normalization of blood glucose levels after resection of the pancreatic lesion were used to confirm the effectiveness of treatment.

In accordance with local guidelines, all patients gave informed consent to the use of anonymous personal data extracted from their medical records for scientific or epidemiological purposes. The local Institutional Review Board approved this retrospective study (FC/dossier 2018-79).

¹⁸F-FDOPA PET/CT: technical features and interpretation criteria

¹⁸F-FDOPA was used in the setting of an approved marketing authorization. All examinations were performed using a combined PET/CT device equipped with time-of-flight measurement capability from 2013 in all three centres. Patients did not fast before radiotracer administration. In all patients, 3–4 MBq/kg of ¹⁸F-FDOPA was intravenously injected 1–2 h after carbidopa premedication (200 mg orally). Pharmaceutical grade carbidopa was purchased from Inresa (Bartenheim, France), and capsules were delivered as formulations prepared according to the guidelines for pharmaceutical compounding of the European Pharmacopoeia (Ph Eur monograph 0755) by the hospital central pharmacy to the nuclear medicine unit. The ¹⁸F-FDOPA PET/CT acquisition protocol included an early acquisition (5 min after injection) centred over the upper abdomen (10-min step) and a delayed whole-body acquisition (starting between 20 and 30 min after injection) from the top of the skull to the upper thighs (3–5 min per step). PET image datasets were reconstructed iteratively (OSEM algorithm) using CT data for attenuation correction.

CT, PET (attenuation-corrected) and PET/CT readings including measurement of quantitative parameters were performed centrally on a dedicated workstation (*syngo.via* VB10B; Siemens). PET/CT images were independently interpreted by two experienced nuclear medicine physicians who were blinded to the results of other imaging investigations. In cases of conflicting results between the two reviewers, a third physician was required to reach a consensus. ¹⁸F-FDOPA PET/CT studies were qualitatively interpreted as positive or negative for insulinoma on both early and delayed acquisitions. A positive pancreatic abnormality was defined as a focal area of increased ¹⁸F-FDOPA uptake compared to surrounding tissue. The number of pathological uptake foci and the topography of uptake abnormalities within the pancreas were evaluated. The pancreas was divided into four main parts with the mesenteric vessels as the reference points, i.e. the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV) [18]: (1) the head, lying to the right of the SMA and the SMV; (2) the isthmus, lying anterior to the SMA and SMV (the SMV joins the splenic vein behind the pancreatic neck to form the portal vein); (3) the body, lying to the left of the SMA and SMV; and (4) the tail, lying between the layers of the splenorenal ligament in the splenic hilum. Areas of increased nonphysiological uptake outside the pancreas were considered as metastatic sites.

In positive PET/CT studies, both tumour maximum standardized uptake values (SUV_{max}) and mean standardized uptake values (SUV_{mean}) of normal pancreatic parenchyma were determined. Tumour SUV_{max} was defined as the SUV_{max} within a spherical volume of interest (VOI) centred on the tumour and including it completely. SUV_{mean} of normal pancreas was the SUV_{mean} within a 1-cm³ spherical VOI positioned so as to avoid areas of biliary stasis. The tumour/normal pancreas ratio (SUV_{ratio}) was calculated as: tumour SUV_{max}/normal pancreas SUV_{mean}. Dopaminergic tumour volume (DTV) of the primary tumour was also defined as the region enclosed by a 40% isocontour around the maximum uptake voxel [19, 20]. By analogy with total lesion glycolysis widely evaluated for ¹⁸F-FDG PET, total lesion ¹⁸F-FDOPA activity (TLDA) was determined as the SUV_{mean} of the tumour VOI multiplied by DTV.

Standard of truth

Histopathological diagnosis of insulinoma was considered as the diagnostic standard of truth. A result was considered true-positive when a preoperative pancreatic abnormality detected by morphological and/or functional imaging topographically matched the pathological findings after surgery. Histological grade was defined according to the eighth edition of the American Joint Committee on Cancer (AJCC) 2017 classification [21]. When available, normalization of blood glucose levels after resection of the pancreatic lesion was used to support a diagnosis of insulinoma and treatment effectiveness. Malignant insulinoma was defined as the presence of histologically proven nodal and/or visceral metastases.

Statistical analysis

The results for continuous data are expressed as means ± standard deviations, medians and ranges, or medians and interquartile ranges (IQR) as appropriate, and categorical variables are presented as numbers and percentages. Differences between groups were assessed using the chi-squared test for categorical variables. Continuous variables were evaluated using the Wilcoxon matched pairs rank test or the Mann-Whitney *U* test as appropriate. Pearson product-moment *r* correlation values were calculated to assess the relationships among variables (¹⁸F-FDOPA quantitative uptake parameters, insulinoma secretory profile, tumour pathological features). Only variables with a statistically significant correlation (*r* ≥ 0.5) are reported. The intraclass correlation coefficient (ICC) was used to evaluate the interobserver reproducibility of both DTV and TLDA. ICC interrater agreement measures were interpreted according to the following criteria: <0.40 poor agreement, 0.40–0.59 fair agreement, 0.60–0.74 good agreement, and 0.75–1 excellent agreement. Statistical significance

was defined as $p < 0.05$. Statistical analysis was performed using GraphPad (Prism6) software.

Results

Patient and tumour characteristics

A total of 35 adult patients with clinical and biological suspicion of insulinoma-related HH examined by dual time-point carbidopa-assisted ^{18}F -FDOPA PET/CT were screened. In eight patients the diagnosis of insulinoma was excluded because of spontaneous normalization of clinical symptomatology and/or biological investigations during follow-up. Three additional patients with type 1 multiple endocrine neoplasia syndrome (MEN-1) who had multiple synchronous functioning and nonfunctioning pancreatic NETs were also excluded. Finally, 24 patients (18 women and 6 men, mean age: 52.5 years, range 21–81 years) were retrospectively included. One patient with a history of surgically treated insulinoma underwent a second PET/CT examination for recurrent HH about 1 year later. Therefore, 25 ^{18}F -FDOPA PET/CT studies were finally retained and analysed. All but one of the patients showed clinical Whipple's triad. In all patients the diagnosis of HH was confirmed by a positive fasting test that showed the following results: fasting-end glucose concentration 0.34 ± 0.08 g/L (normal value for nondiabetic patients >0.50 g/L), fasting-end insulin level 23.8 ± 21.7 mUI/L (normal value <17 mUI/L) and fasting-end C-peptide level 3.9 ± 2.3 ng/mL (normal value <0.8 ng/mL). In all patients except one the diagnosis of insulinoma was histologically confirmed after surgical removal of the pancreatic lesion. Moreover, 4 of 24 patients, presented with pathological proof of nodal and liver metastatic involvement. In one patient with metastatic spread, the disease was considered inoperable.

In the studied population, the median (IQR) sizes of all lesions, only benign insulinomas, and only malignant tumours were 18 mm (7 mm), 16 mm (7 mm) and 76.5 mm (10.75 mm), respectively. The tumour was located in the pancreatic head in four studies, the isthmus in two studies, the body in ten studies and the tail in nine studies. Benign insulinomas were grade 1 in 14 studies and grade 2 in 6 studies. In grade 2 tumours, the Ki-67 index ranged from 3% to 5%. One malignant insulinoma was grade 1 (Ki-67 1%) and three were grade 2 (Ki-67 3%, 4% and 5%). In one patient, insulinoma was related to MEN-1 syndrome, and in the remaining patients it was sporadic.

At the time of PET/CT, five patients were receiving treatment with diazoxide alone, two with both diazoxide and prednisone, and one with SSAs.

Preoperative work-up included three-phase contrast-enhanced abdominal CT and contrast-enhanced pancreatic MRI scans in all patients. EUS was performed in 19 patients

and allowed insulinoma diagnosis by fine-needle aspiration biopsy in 12 patients. EUS contributed to the final diagnosis in three patients without pancreatic abnormalities on CT or MRI. ^{18}F -FDOPA PET/CT localized insulinoma in 21 of the 25 studies, The insulinoma was localized in 18 of the 25 CT studies and in 17 MRI studies. CT and MRI were considered positive concordant in 13 studies and positive discordant in 9 studies. Conventional imaging failed to identify any pancreatic abnormality in three studies. Patient characteristics are presented in detail in Table 1.

^{18}F -FDOPA PET/CT findings

On visual examination, physiological pancreatic uptake of ^{18}F -FDOPA was slight and lower than that of healthy hepatic parenchyma. Thus, carbidopa premedication was considered effective in all PET/CT studies. Moreover, ^{18}F -FDOPA pancreatic uptake was significantly lower on delayed images than on early images ($p = 0.0005$). No patients reported early or delayed undesirable effects related to carbidopa premedication.

In the entire population, CT and MRI localized 18 (72%) and 17 (68%) of 25 pancreatic tumours. In the same patients, early and delayed PET/CT were able to detect insulinoma in 21 (84%) and 17 (68%) of the 25 studies (Fig. 1, Table 3). Four insulinomas (19%) were detected only on early PET/CT (Fig. 2). All the ^{18}F -FDOPA PET/CT scan interpretations by the nuclear medicine physicians were concordant in the per-patient analysis (PET/CT positive or negative for insulinoma localization) and in the per-lesion analysis (pancreatic lesion topography). In no case was the third physician required to reach a consensus as to the positivity or negativity of a PET/CT result. However, the interpretation of lesion topography was incongruent between the blinded readers in two patients (patients 19 and 20) so that the third reader was required to reach a consensus. Overall, tumour localization was concordant among PET/CT results, surgical exploration and pathology. No false-positive PET/CT results were obtained in relation to pathological findings.

Considering only benign insulinomas, the detection rates of early and delayed PET/CT, CT and MRI were 81% (17/21), 62% (13/21), 67% (14/21) and 62% (13/21), respectively. Finally, ^{18}F -FDOPA PET/CT failed to localize four benign insulinomas, one of the pancreatic head, two of the pancreatic body, and one of the pancreatic tail (9 mm, 11 mm, 18 mm and 20 mm, respectively). Of the four insulinomas not detected by ^{18}F -FDOPA PET/CT, two were localized by CT and one by MRI. In three of four patients with malignant insulinomas (patients 8, 15 and 21; Table 1) morphological imaging and PET/CT both showed multiple hepatic metastases. In the last of these patients (patient 11; Fig. 3), retrospective analysis of hepatic MRI imaging guided by PET/CT allowed the detection of parenchymal nodules of a few millimetres.

Table 1 Studied population of patients with histologically proven insulinoma and related hyperinsulinaemic hypoglycaemia

Patient number	Age (years)	Sex	Conventional imaging		Tumour		PET/CT		Medical treatment	Final diagnostic procedure	Final diagnosis	
			CT	MRI	Size (mm)	Location	Early	Delayed			Insulinoma	Grade
1	51	F	Positive	Negative	6	Body	Positive	Positive	None	Pancreatic surgery ^b	Benign	1
2	30	M	Negative	Positive	11	Tail	Positive	Negative	None	Pancreatic surgery	Benign	2
3	48	F	Negative	Positive	12	Head	Positive	Negative	None	Pancreatic surgery	Benign	1
4	81	F	Positive	Negative	20	Body	Positive	Positive	None	Pancreatic surgery	Benign	1
5 ^a	44	M	Positive	Positive	18	Body	Negative	Negative	Diazoxide	Pancreatic surgery	Benign	1
			Positive	Negative	16	Body	Positive	Negative	None	Pancreatic surgery	Benign	2
6	40	F	Negative	Positive	11	Body	Negative	Negative	None	Pancreatic surgery	Benign	2
7	62	F	Negative	Negative	9	Tail	Positive	Positive	Prednisone	Pancreatic surgery	Benign	1
8	41	F	Positive	Positive	78	Body	Positive	Positive	Lanreotide	US-guided biopsy (pancreas and lymph node metastasis)	Malignant	1
9	48	M	Positive	Positive	20	Tail	Negative	Negative	None	Pancreatic surgery	Benign	1
10	73	F	Positive	Negative	13	Body	Positive	Positive	Diazoxide/prednisone	Pancreatic surgery	Benign	1
11	68	M	Positive	Positive	75	Body	Positive	Positive	Diazoxide	Pancreatic and hepatic surgery	Malignant	2
12	21	M	Positive	Positive	19	Tail	Positive	Positive	None	Pancreatic surgery	Benign	1
13	58	F	Negative	Negative	9	Head	Negative	Negative	Diazoxide/prednisone	Pancreatic surgery	Benign	2
14	65	F	Positive	Negative	18	Tail	Positive	Positive	None	Pancreatic surgery	Benign	1
15	54	F	Positive	Positive	85	Tail	Positive	Positive	Diazoxide	Pancreatic surgery	Malignant	2
16	50	F	Positive	Positive	15	Head	Positive	Positive	None	Pancreatic surgery	Benign	1
17	53	F	Negative	Positive	14	Tail	Positive	Positive	None	Pancreatic surgery	Benign	1
18	42	F	Positive	Positive	17	Body	Positive	Positive	None	Pancreatic surgery	Benign	1
19	43	F	Negative	Negative	15	Isthmus	Positive	Negative	None	Pancreatic surgery	Benign	2
20	70	M	Positive	Positive	40	Isthmus	Positive	Positive	None	Pancreatic surgery	Benign	2
21	52	F	Positive	Positive	51	Body	Positive	Positive	Diazoxide	Pancreatic and hepatic surgery	Malignant	2
22	39	F	Positive	Positive	18	Tail	Positive	Positive	None	Pancreatic surgery	Benign	1
23	65	F	Positive	Positive	20	Tail	Positive	Positive	None	Pancreatic surgery	Benign	1
24	63	F	Positive	Positive	22	Head	Positive	Positive	Diazoxide	Pancreatic surgery	Benign	1

US ultrasound

^a Patient 5 underwent two PET/CT examinations, the second for recurrent HH (insulinoma relapse) after surgical treatment

^b Clinical and biological follow-up of at least 3 months was obtained after pancreatic surgery

Pathological diagnosis of multiple liver metastases was made after extensive surgery.

Benign insulinomas showed significantly higher SUVmax on early PET/CT images than on delayed images ($p = 0.05$). In contrast, malignant tumours showed higher SUVmax (but not significantly) on delayed PET/CT images. The lack of statistical significance might be due to the limited number of patients studied. As shown in Table 2, neither benign nor malignant insulinomas showed significant differences in SUVratio, DTV or TLDA between early and delayed PET/CT images. In our cohort, malignant insulinomas were significantly larger than benign tumours ($p = 0.01$) and showed significantly higher early and delayed SUVmax, SUVratio, DTV and

TLDA (Table 2). There were no significant differences between grade 1 and 2 benign insulinomas.

The false-negative rate of ¹⁸F-FDOPA PET/CT for tumour detection was 22% (2 of 9 studies) in patients receiving treatment for hypoglycaemic symptoms at the time of examination and 12.5% (2 of 16 studies) in patients not receiving treatment. Benign insulinomas positive on PET/CT showed no significant differences in tumour PET metabolic parameters between patients receiving and not receiving treatment.

In the ICC analysis, the interobserver agreement coefficients for both DTV and TLDA were more than 0.95 for both early and delayed PET acquisitions, indicating that these metabolic indexes were highly reproducible. The

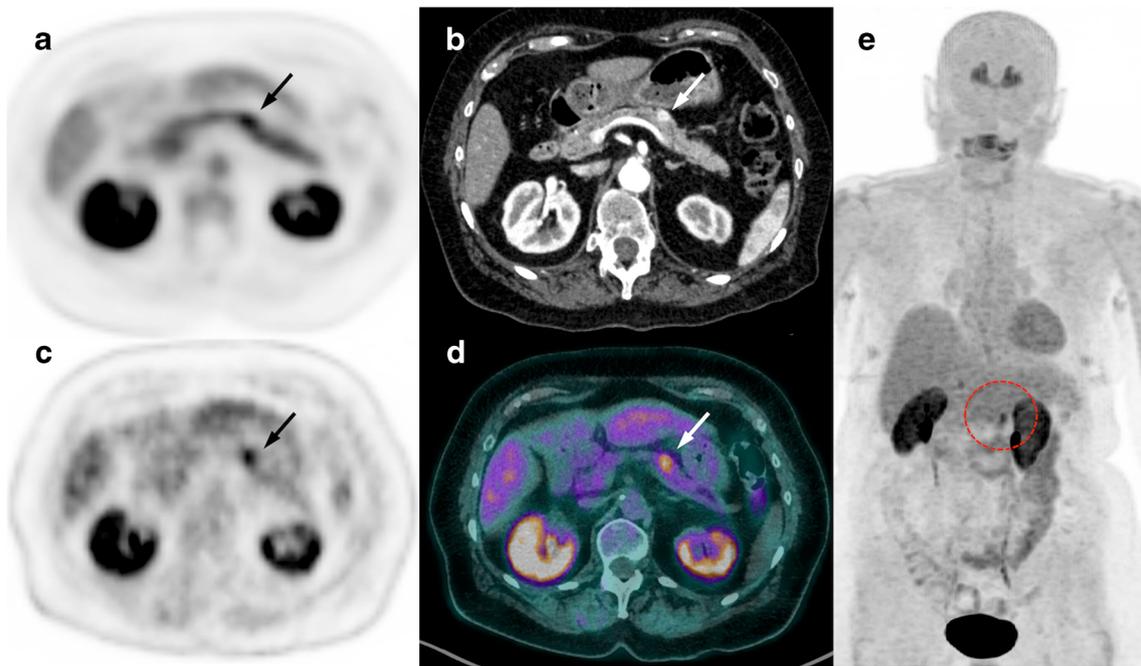


Fig. 1 Contrast-enhanced CT and carbidopa-assisted ^{18}F -FDOPA PET/CT imaging in a 73-year-old woman with hyperinsulinaemic hypoglycaemia-related insulinoma (patient 10; Table 1). The arterial phase CT image (b) shows intense contrast enhancement of a 13-mm

rounded body tumour (arrow). Both the early (a) and delayed (c–e) PET images show pathological focal uptake (a SUVmax 6.3, c–e SUVmax 5.3). Note the faint carbidopa-related ^{18}F -FDOPA uptake in normal pancreas improving lesion detectability (red circle)

relationships among ^{18}F -FDOPA quantitative uptake parameters (assessed by the most experienced nuclear medicine physician), biological secretory profiles, and pathological tumour characteristics were also investigated in the overall population. Fasting-end insulin levels were significantly correlated with delayed SUVmax ($r = 0.5$, $p =$

0.01) and delayed SUVratio ($r = 0.6$, $p = 0.002$). Fasting-end C-peptide levels were significantly correlated with delayed SUVratio ($r = 0.5$, $p = 0.03$). Finally, delayed SUVmax, early and delayed SUVratio, and delayed TLDA were significantly correlated with tumour size ($r = 0.5$, $p = 0.015$; $r = 0.5$, $p = 0.011$; $r = 0.7$, $p = 0.001$; $r = 0.5$,

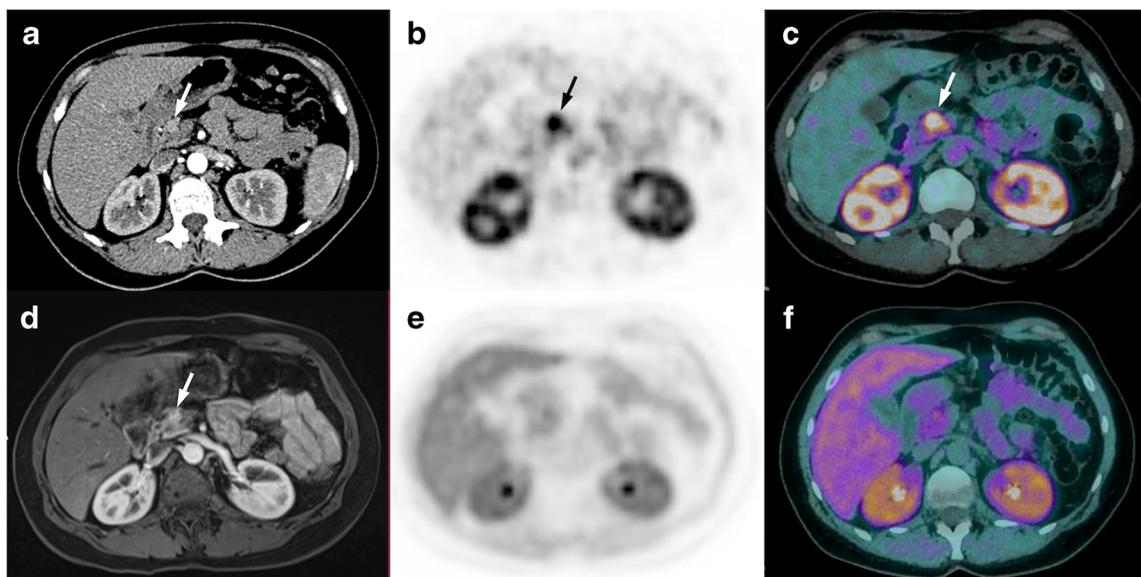


Fig. 2 Conventional imaging and carbidopa-assisted ^{18}F -FDOPA PET/CT imaging in a 44-year-old man with recurrent insulinoma (patient 5, second study; Table 1). The arterial phase contrast-enhanced CT image (a) and the T1-weighted fat-saturated MRI image (d) show focal contrast

enhancement of a 16-mm insulinoma of the pancreatic body (arrows). The early PET/CT images (b, c) clearly show the insulinoma (SUVmax 8.9). On the delayed images (e, f) the lesion has completely disappeared

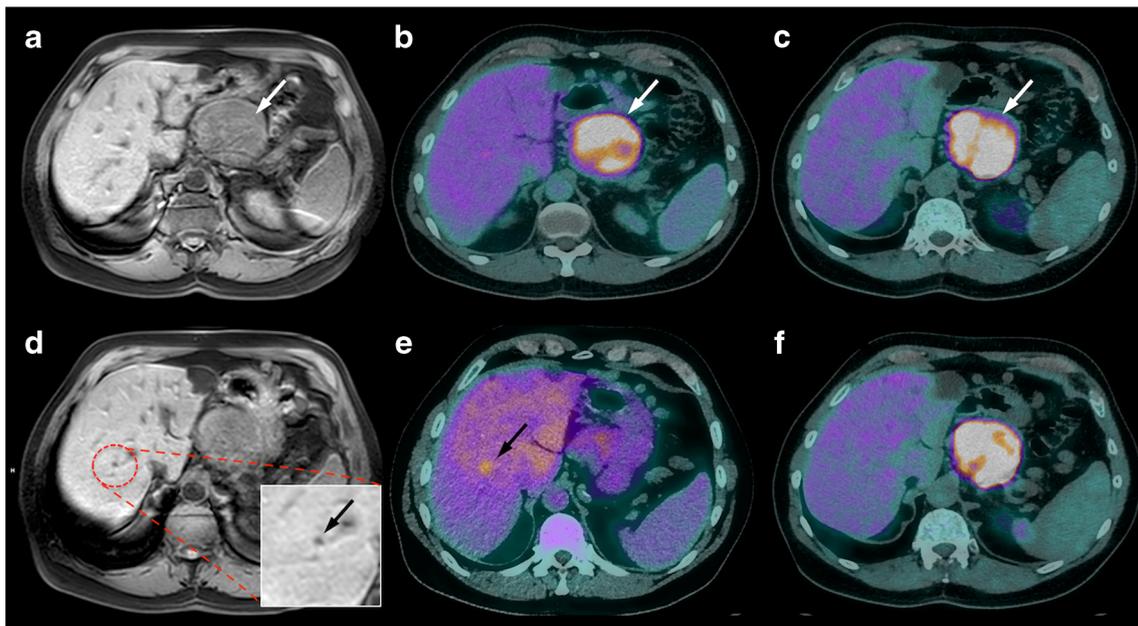


Fig. 3 MRI and carbidopa-assisted ^{18}F -FDOPA PET/CT imaging in a 68-year-old man with malignant insulinoma (patient 11, Table 1). The MRI image (a) shows a 75-mm rounded body pancreatic mass (arrow). The early (b) and delayed (c) PET/CT images show intense and heterogeneous ^{18}F -FDOPA uptake (SUVmax 44.7 and 63.1, respectively). The early PET image (e) shows pathological focal ^{18}F -FDOPA uptake in the

eighth hepatic segment (arrow). On the delayed image (f) the pathological focal ^{18}F -FDOPA uptake has disappeared. The MRI image (d) analysed retrospectively confirms the presence of a parenchymal nodule of a few millimetres (red circle). A pathological diagnosis of malignant insulinoma with multiple liver metastases was made after extensive surgery

$p = 0.014$, respectively). Interestingly, there was a slight but significant inverse correlation between fasting-end

glucose concentration and delayed SUVratio ($r = -0.4$, $p = 0.04$).

Table 2 ^{18}F -FDOPA quantitative uptake parameters in benign and malignant insulinomas

	Healthy pancreas	Benign insulinomas	Malignant insulinomas	p value
SUVmax				
Early		6.3 ± 2.3 (1.8–9.5)	24.7 ± 14.6 (9.6–44.7)	0.0003
Delayed		5.0 ± 1.8 (2.2–8.3)	34.1 ± 20.1 (19.5–63.1)	0.0001
p value		0.05	0.12	
SUVmean				
Early	3.0 ± 0.9 (1.9–6.6)			
Delayed	3.5 ± 0.5 (1.1–3.5)			
p value	0.0001			
SUVratio				
Early		2.4 ± 1.1 (0.5–4.8)	8.6 ± 3.7 (3.9–12.7)	0.001
Delayed		2.5 ± 1.2 (1.1–5.3)	16.3 ± 11.4 (4.8–31.5)	0.0005
p value		0.9	0.12	
DTV				
Early		7.8 ± 5.9 (1.9–26.4)	65.4 ± 51.3 (12.5–135)	0.0013
Delayed		6.7 ± 5.5 (1.3–22)	51 ± 38.9 (5.6–99.3)	0.0072
p value		0.11	0.12	
TLDA				
Early		42.9 ± 58.7 (3.3–270)	771.5 ± 419.2 (301.6–1313)	0.0002
Delayed		29.1 ± 30.4 (5.8–131.8)	697.8 ± 430.3 (196.3–1240)	0.0002
p value		0.10	0.37	

The data are expressed as means \pm standard deviation (range)

SUV standardized uptake value, DTV dopaminergic tumour volume, TLDA total lesion dopaminergic activity

Table 3 Results of presurgical imaging investigations for the detection of pancreatic insulinomas

	Benign and malignant insulinomas detected	Benign insulinomas detected
Three-phase contrast-enhanced CT	18/25 (72%)	14/21 (67%)
Contrast-enhanced MRI	17/25 (68%)	13/21 (62%)
PET/CT		
Early	21/25 (84%)	17/21 (81%)
Delayed	17/25 (68%)	13/21 (62%)

Discussion

This study confirmed that the combination of oral carbidopa premedication and early pancreatic imaging is a safe and accurate diagnostic alternative in patients with HH providing a high rate of detection of insulinoma. To the best of our knowledge, this is the largest study that has evaluated ^{18}F -FDOPA PET imaging in patients with HH and pathologically proven insulinoma. ^{18}F -FDOPA PET/CT was able to detect both benign and malignant insulinomas and to correctly assess tumour spread in patients with metastases. ^{18}F -FDOPA PET/CT identified 84% of insulinomas, including metastatic tumours in four patients. Moreover, the study provided new insights into the relationships between tumour secretion and imaging phenotype in insulinomas.

^{18}F -FDOPA remains a versatile radiotracer for NET imaging but the imaging protocol has to be suited to each individual situation [22]. Insulinomas [10, 11], medullary thyroid carcinomas [23, 24] and nonfunctioning pancreatic neuroendocrine tumours [25] are prime examples of NET that require specific protocols to increase sensitivity. In these GEP-NET, early imaging can facilitate tumour detection and increase diagnostic confidence regarding interpretation of liver and abdominal regions in patients with metastatic disease due to limited activity in both the hepatobiliary and renal systems. In patients with benign lesions, the intensity of ^{18}F -FDOPA uptake in the insulinoma was significantly lower in delayed PET images than in early images. Interestingly, a slight decline in ^{18}F -FDOPA uptake intensity during a 20-min dynamic acquisition has also been reported in a mouse xenograft model of insulinoma [12]. Obviously, the preclinical model significantly differs from benign human insulinoma and therefore any comparison would need to be validated before firm conclusions can be drawn.

Kauhanen et al. [14] raised concern about the risk of false-negative ^{18}F -FDOPA PET/CT results following carbidopa administration in two patients with insulinoma. However, we have recently found that carbidopa did not seem to affect ^{18}F -FDOPA accumulation in vitro in RIN-m5f beta cells but improved insulinoma imaging in vivo in a xenograft mouse model [12]. In the present study, we found a higher rate of

detection of insulinoma by ^{18}F -FDOPA PET/CT than that reported by Tessonier et al. [16], and more recently, by Nakuz et al. [17]. In both studies, ^{18}F -FDOPA PET/CT was performed without carbidopa premedication. Interestingly, Nakuz et al. [17] highlighted the usefulness of iodinated contrast medium administration during the PET/CT study. These authors performed ^{18}F -FDOPA PET with contrast-enhanced CT about 20 min after ^{18}F -FDOPA injection in ten patients with histologically proven insulinoma. The sensitivity of ^{18}F -FDOPA PET was 50%, increasing to 70% when coupled with contrast-enhanced CT. Similarly, in our population, two insulinomas were missed by PET (i.e. false-negative) and correctly localized by preoperative CT, emphasizing the role of contrast-enhanced CT integrated with PET/CT as a “one-stop shop” insulinoma imaging.

^{18}F -FDOPA PET/CT failed to detect four benign insulinomas. No definitive explanation for these false-negative results can be provided. Tumour size was about 1 cm in all cases, thus the partial volume effect does not seem to have been responsible for these false-negative findings. Perhaps respiratory gating could be done to improve the detection of small insulinomas. No evident differences in histological or biological profile compared with PET-positive lesions were found. Nonetheless, intercurrent medication preventing pancreatic insulin release was not withdrawn before PET/CT in two of four patients because of the risk of severe hypoglycaemia (Table 1). In children with congenital hyperinsulinism, Ribeiro et al. [26] suggest that treatment should be withdrawn 72 h before PET examination, with normoglycaemia maintained by glucose infusion and blood glucose monitoring. Other authors also encourage withdrawal of medication including diazoxide, prednisone and SSAs about 24 h before PET in adults [27].

In our study, assessment of both TLDA and DTV represented a significant workload, without significant clinical impact. No independent information was afforded by TLDA or DTV for topographical diagnosis of insulinoma, and the inadequate follow-up limited further prognostic considerations. Since the L-amino acid transporter system (LAT) is regulated by the mTOR-signalling pathway, ^{18}F -FDOPA PET could be an attractive molecular tool for evaluating therapeutic responses to mTOR inhibitors [28, 29] or to specific LAT family

inhibitors/modulators. Thus, quantitative biomarkers such as TLDA and DTV could be useful for monitoring tumour metabolic burden and treatment efficacy of targeted molecular therapy in patients with malignant insulinomas. This will be addressed by an ongoing study.

Amodru et al. [30] recently described the correlation between ^{18}F -FDOPA uptake in pheochromocytomas, and genetic phenotype and biochemical tumour secretion. Similarly, Fiebrich et al. [31] found that metabolic tumour burden on ^{18}F -FDOPA PET was positively correlated with the amount of serotonin secretion in patients with gastrointestinal neuroendocrine tumours. To our knowledge, the existing relationships among ^{18}F -FDOPA uptake, biological secretory profile and pathological characteristics of insulinoma have not yet been explored. In our patients, tumour ^{18}F -FDOPA uptake was correlated with lesion size, and fasting-end concentrations of both insulin and C-peptide, confirming that ^{18}F -FDOPA uptake reflects the functional activity and hormone secretion of the tumour.

^{18}F -FDOPA, ^{68}Ga -DOTA peptides [9, 32] and radiolabelled GLP-1 analogues [7, 33] have not been specifically compared as PET/CT tracers in patients with insulinoma. In a recent study by Antwi et al. [7], ^{68}Ga -DOTA-exendin-4 PET/CT was found to be able to localize insulinoma in a subgroup of five patients with negative ^{18}F -FDOPA PET/CT results. Unfortunately, carbidopa was not administered and early PET images were not obtained, so that definitive conclusions could not be drawn.

Although the histopathological standard of truth used in this study is a robust criterion, the retrospective design of the study implies a potential bias in patient selection and is its main limitation. Indeed, only ^{18}F -FDOPA PET/CT in patients with a proven diagnosis of insulinoma and tumour localization (subsequently treated surgically) were retrospectively evaluated, suggesting that only patients with a high rate of positive molecular or morphological imaging were a priori selected. This could have affected the rate of detection of insulinoma. Moreover, the patients selected were from three independent institutions equipped with different PET/CT systems. Nevertheless, the ^{18}F -FDOPA PET/CT examinations were performed following the same imaging protocol, ensuring reproducibility. Despite these limitations, this study is the largest available and consolidates the role of ^{18}F -FDOPA PET/CT in patients with HH-related insulinoma.

In conclusion, the present study showed that ^{18}F -FDOPA PET/CT combined with carbidopa premedication and early pancreatic imaging is a valuable diagnostic option in patients with insulinoma when GLP1R-based imaging is not available. Three-phase contrast-enhanced CT integrated with PET/CT as “one-stop shop” could potentially be used as a first-line imaging approach in patients with suspicion of insulinoma, and deserves further study.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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