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Comparison of 6-¹⁸F-Fluoro-L-DOPA, ¹⁸F-2-Deoxy-D-glucose, CT, and MRI in patients with pancreatic neuroendocrine tumors with von Hippel-Lindau disease

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Abstract

Introduction—There is limited data on the utility of 6-¹⁸F-Fluoro-L-3,4-dihydroxyphenylalanine (¹⁸F-DOPA) and ¹⁸F-2-Deoxy-D-glucose (¹⁸F-FDG) in the workup of patients with pancreatic neuroendocrine tumors (PNETs). The aim of our study was to determine the accuracy of ¹⁸F-DOPA and ¹⁸F-FDG to detect PNETs in patients with von Hippel-Lindau disease (VHL).

Methods—69 patients with a diagnosis of VHL and pancreatic lesion(s) were prospectively studied using CT, MRI, ¹⁸F-FDG, and ¹⁸F-DOPA. Clinical, genetic, and laboratory characteristics were analyzed to determine association with imaging study results.

Results—40 patients underwent evaluation by all four modalities, 98 PNETs and 55 PNETs were identified on CT and MRI, respectively. Only 11 of the 98 lesions (11%) were positive on ¹⁸F-DOPA and 45 of the 98 (46%) lesions were positive on ¹⁸F-FDG. There were 13 ¹⁸F-DOPA and 26 ¹⁸F-FDG avid extra-pancreatic lesions. One patient underwent resection of an ¹⁸F-DOPA avid extra-pancreatic lesion in the lung, with pathology demonstrating a NET. There was no association between ¹⁸F-DOPA and ¹⁸F-FDG avidity and tumor size, age, sex, VHL mutation, or serum chromogranin A level.

Conclusion—¹⁸F-FDG and MRI may be adjuncts to CT scan in identifying PNETs and metastatic disease. ¹⁸F-DOPA has limited value in identifying PNETs in patients with VHL but may be useful for identifying extra-pancreatic NET lesions.

Keywords

¹⁸F-DOPA; ¹⁸F-FDG; von Hippel-Lindau disease; pancreatic neuroendocrine tumor

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Introduction

Von Hippel-Lindau (vHL) disease is a rare inherited genetic disorder manifested by development of a myriad of tumors in multiple organs. It affects approximately 1 in 36,000 births and it has an autosomal dominant inheritance pattern. Approximately 20% of vHL cases are due to *de novo* germline mutation without any family history of vHL.¹ Some of the common organs involved in vHL include the central nervous system in the form of benign hemangioblastomas, pancreas in the form of cysts or solid pancreatic neuroendocrine tumors, and other manifestations may involve the inner ear (endolymphatic sac tumors), kidneys (cysts or clear cell renal cell carcinoma), epididymus (epididymal cysts), and adrenal glands (pheochromocytoma).²

Pancreatic lesions may develop in 35-77% of patients with vHL and most of them present as benign cysts mainly comprised of simple cysts or rarely serous cystadenomas.³ Although, these lesions have no malignant potential, they can cause symptoms (e.g. pain, gastrointestinal obstruction) due to their size or endocrine dysfunction due to destruction of the normal pancreatic parenchyma leading to diabetes mellitus and pancreatic exocrine insufficiency. Solid lesions, on the other hand, are less common (5-17%) but may be malignant in up to 17% of patients.⁴⁻⁶ They are derived from pancreatic islet cells and all of them are thought to be non-functional. Blansfield et al⁴ based on clinical, genetic, and radiographic factors reported that tumor size greater than 3cm, presence of exon 3 mutation, and doubling time less than 500 days were associated with malignant PNETs.

Different imaging modalities have been used to detect PNETs. Computed tomography scan (CT) has been the most widely used modality with sensitivity of 29-94% and provides higher sensitivity when both arterial and portal venous phases are performed.⁷⁻⁹ The wide range in sensitivity is primarily due to many small PNETs being missed by CT scans. It is estimated that CT scans and magnetic resonance imaging (MRI) are able to localize more than 50% of tumors that are greater than 3cm in diameter but only 5% of tumors measuring less than 1cm in size.¹⁰ Positron emission tomography (PET) scan is becoming more widely used and may be a useful localizing modality for neuroendocrine tumors as different radio-labeled substance can be used as metabolic substrate. Although ¹⁸F-2-Deoxy-D-glucose (¹⁸F-FDG) PET is the most widely used and accepted type of PET in clinical oncology, it has limited use in well-differentiated tumors such as neuroendocrine tumors due to their low expression of glucose transporters and low proliferative activity.¹¹⁻¹² More recently, two particular modalities of PET [6-¹⁸F-Fluoro-L-3,4-dihydroxyphenylalanine (¹⁸F-DOPA) and ¹¹C-5-hydroxytryptophan (¹¹C-5-HTP)] have gained increased attention in localization of neuroendocrine tumors as these tumors have the ability to produce biogenic amines and polypeptide hormones and they take up and decarboxylate their amine precursors, L-dihydroxyphenylalanine and 5-hydroxytryptophan.¹²⁻¹⁴ ¹⁸F-DOPA has a sensitivity of 65-96% for detecting carcinoid tumors but is much less sensitive for detecting pancreatic islet cell tumors.¹⁵ Koopmans et al¹³ found that ¹¹C-5-HTP is superior to ¹⁸F-DOPA in detecting islet cell tumors. Although these modalities have been studied in a variety of neuroendocrine tumors, ¹⁸F-FDG and ¹⁸F-DOPA have not been previously studied in PNETs in the setting of vHL and in a large enough cohort to better ascertain the accuracy of these imaging studies. Thus, the goals of our study were to: (1) evaluate the accuracy of ¹⁸F-FDG and ¹⁸F-DOPA compared to CT and MRI to detect PNETs in patients with vHL; and (2) determine any variables associated with ¹⁸F-FDG and ¹⁸F-DOPA positivity.

Materials and Methods

Patients

87 patients with vHL were seen in the endocrine surgery clinic at the National Institutes of Health from March 2010 to January 2011. Patients were evaluated on a protocol approved by our Institutional Review Board. Their demographic information and imaging studies were obtained prospectively and a thorough history and physical along with laboratory studies were performed during the same visit.

Imaging studies

CT scan—All the patients underwent fine-cut multi-phase helical CT scan with both arterial and portal venous phase unless there was contraindication for administration of intravenous (IV) contrast such as renal insufficiency, patient allergy to contrast dye, or patient refusal. The diagnosis of PNETs was made on the arterial phase of the CT scan. Identification and measurement of the PNETs were performed by three independent readers and the size of the PNETs was averaged among the three readers.

MRI scan—All the patients underwent MRI of the abdomen unless there was contraindication for administration of gadolinium or patient refusal. MRI scans included axial T2 with and without fat saturation, axial T1 in and out of phase and dynamic thrive during infusion of contrast, followed by delayed axial and coronal post-contrast scans. PNETs were identified on early arterial phase of the contrast administration. All the MRI scans were reviewed by endocrine surgery team and cross-checked with the official radiology report.

^{18}F -FDG PET—All patients with solid PNETs underwent ^{18}F -FDG unless there was contraindication or patient refusal. The scans were performed approximately 60 minutes after the administration of 10 mCi of intravenous ^{18}F -FDG for patients under 200 pounds of weight and 15 mCi of intravenous ^{18}F -FDG for patients over 200 pounds of weight. The patients were scanned from their skull base to the mid thighs. A non-contrast, non-diagnostic CT scan was used for attenuation and anatomical localization. Maximal standardized uptake values (SUV max) were calculated based on the patients' body weight and ^{18}F -FDG-avid foci both intra- and extra-pancreatic were reviewed and reported by nuclear medicine radiologist(s).

^{18}F -DOPA PET—All patients with solid PNETs were offered to undergo ^{18}F -DOPA PET. The scans were performed approximately 60 minutes after the administration of 12 mCi of intravenous ^{18}F -DOPA and the patients were scanned from the top of the head to the upper thighs. All the patients received 200mg of carbidopa one hour prior to the injection of ^{18}F -DOPA with the exception of the first patient enrolled onto the protocol. Transmission images were performed with a GE-68 source and used for attenuation correction. Attenuation-corrected (AC) and non-attenuation-corrected (NAC) images were reviewed and maximal standardized uptake values (SUV) were reported by an ^{18}F -DOPA PET-dedicated nuclear medicine radiologist.

Biochemical analysis

All the patients underwent laboratory studies prior to the acquisition of imaging studies. These studies included complete blood count, complete serum chemistries including amylase, lipase, pancreatic polypeptide, fasting insulin, vasoactive intestinal peptide, chromogranin A, glucagon, 5-HIAA, and serum and urine metanephrines and catecholamines.

Surgical intervention and histology

Patients who met the surgical criteria underwent resection of their PNETs. The tumors were resected if they were greater than 3cm (or greater than 2.0 cm in the head of the pancreas). All the interventions were performed on a protocol approved by our Institutional Review Board. The operative procedure depended on the tumor size and location. Those patients with PNETs that did not meet the surgical criteria were instructed to continue serial scans and surveillance annually. Pathology of the PNETs were classified based on the World Health Organization (WHO) classification^{10, 16} and MIB1 staining was reported as the surrogate for Ki67 and as the marker of proliferation index.¹⁷

Results

Patient demographics and clinical characteristics are summarized in Table 1. Of 87 patients with vHL related pancreatic lesions, 69 patients were found to have solid lesion(s) of the pancreas (PNETs). 18 patients without PNETs were excluded from the analysis. 66 CTs, 60 MRIs, 58 ¹⁸F-FDG-PETs, and 42 ¹⁸F-DOPA PETs were performed in 69 patients and 40 patients were evaluated with all 4 modalities (Figure 1). Among the patients who underwent evaluation by all four modalities, 98 PNETs and 55 PNETs were identified on CT and MRI, respectively. Only 11 of the 98 lesions (11%) were positive on ¹⁸F-DOPA and 45 of the 98 (46%) lesions were positive on ¹⁸F-FDG. Comparison of these 4 modalities is summarized in Table 2. Three of the 55 PNETs that were identified on MRI were not visualized on CT scan and three patients were found to have arterially enhancing lesions in the liver, which were not visualized on CT scan. Only one of those 3 patients underwent resection of the arterially enhancing liver lesion along with the PNET, demonstrating metastatic disease to the liver. One of the 45 ¹⁸F-FDG avid lesions was not visualized on CT scan. ¹⁸F-FDG was positive in peri-pancreatic lymph node(s) in 2 out of 3 patients who had evidence of lymph node metastasis on the final pathology. All the ¹⁸F-DOPA avid pancreatic lesions were also avid on ¹⁸F-FDG. Figure 2 depicts examples of ¹⁸F-FDG avid and ¹⁸F-DOPA avid lesion in the uncinate process from the same patient.

There were 13 ¹⁸F-DOPA and 26 ¹⁸F-FDG avid extra-pancreatic and extra-renal lesions and most of them were in the adrenal glands. 6 out of 7 patients with ¹⁸F-DOPA avid adrenal lesions had normal serum and urine catecholamines and metanephrines. One patient with an abnormal catecholamine value had only minimally elevated 24-hour urine norepinephrine, with a normal I¹²³-meta-iodobenzylguanidine (I¹²³-MIBG) scan. One patient underwent resection of an ¹⁸F-DOPA avid extra-pancreatic lesion in the lung, with pathology demonstrating a neuroendocrine tumor.

Germline mutation status was available for 81/87 patients and mutation status was available for 10/12 of the patients that underwent surgical resection of the PNETs. There was no association between Exon 3 mutation status with tumor histology, presence of liver or lymph node metastasis, ¹⁸F-DOPA, or ¹⁸F-FDG avidity. The average size of the PNETs on CT scan was 1.3±0.91 (Table 1) and the average tumor sizes on ¹⁸F-FDG and ¹⁸F-DOPA were 1.8±0.97 and 1.5±0.54, respectively (Table 3). There was no correlation between ¹⁸F-FDG and ¹⁸F-DOPA avidity and tumor size, age, sex, and serum chromogranin A levels.

12 patients underwent resection of their PNETs. The surgical intervention, histological, and radiological findings are summarized in Table 4. Most of the lesions (10/12) were avid on ¹⁸F-FDG, however, there was no correlation between the size of the lesions and the SUV values, with pearson's correlation value of $r = -0.22$. Most of the lesions (10/12) were negative on ¹⁸F-DOPA. There were only two patients with elevated serum chromogranin A levels. Interestingly, the patient with the highest serum chromogranin A level of 1,105 ng/ml had a PNET that was avid on both ¹⁸F-FDG and ¹⁸F-DOPA. However, ¹⁸F-FDG and ¹⁸F-

DOPA were negative in the patient with the second highest serum chromogranin A level. There was no correlation between the ^{18}F -FDG avidity with the level of MIB1 and tumor mitotic index.

Discussion

In this study, we compared the two most commonly utilized imaging modalities (i.e. CT scan and MRI scan) with two experimental imaging modalities (i.e. ^{18}F -FDG and ^{18}F -DOPA) for the evaluation of PNETs in the setting of vHL. Our study demonstrated that the vast majority (89%) of PNETs were not detected by ^{18}F -DOPA PET in patients with vHL. All the ^{18}F -DOPA avid PNETs were identified on CT scans and were also ^{18}F -FDG avid, suggesting that ^{18}F -DOPA has no role in identifying additional PNETs that may have been missed by other imaging modalities. In addition, there were two patients with known metastatic disease to the liver and the ^{18}F -DOPA failed to demonstrate any lesions in the liver, indicating its inability to detect metastatic disease. ^{18}F -FDG, on the other hand, identified approximately half (46%) of PNETs and also identified 1 PNET that was not initially seen on CT scan. ^{18}F -FDG was also positive in the peri-pancreatic lymph node(s) in 2 out of the 3 patients who had evidence of lymph node metastasis on the final pathology. MRI was able to identify three lesions that were not visualized on CT scan. MRI also demonstrated arterially-enhancing liver lesions in six patients, two of them with known metastatic disease to the liver, and three of them which were not visualized on the CT scan. We also found no association between ^{18}F -FDG and ^{18}F -DOPA avidity and clinical factors such as sex, size of the tumor, mutational status, and serum chromogranin A levels. There was no discernable association between Exon 3 mutation status with presence of metastatic disease as previously described⁴, although it is impossible to extrapolate any conclusion due to the small number of patients who underwent surgical resection.

There were 13 extra-pancreatic lesions demonstrated on ^{18}F -DOPA and most of them were in the adrenal glands. All the patients with ^{18}F -DOPA avid adrenal lesions (with exception of one patient with minimally elevated 24-hour urine norepinephrine) had normal serum and urine catecholamines. There is a limited number of studies demonstrating utility of ^{18}F -DOPA in localizing pheochromocytomas and one of the initial studies by Hoegerle et al¹⁸ observed a 100% sensitivity in pheochromocytoma detection by ^{18}F -DOPA. A more recent study by Fottner et al¹⁹ demonstrated that ^{18}F -DOPA is superior to I¹²³-MIBG in identifying extra-adrenal and familial pheochromocytomas. It is well-established that patients with vHL are susceptible to developing pheochromocytoma, however, as none of these patients with ^{18}F -DOPA avid adrenal lesions underwent resection of these lesions, it is difficult to conclude whether these lesions may indicate evidence of sub-clinical pheochromocytomas. Only one patient underwent resection of an ^{18}F -DOPA avid extra-pancreatic lesion (in the lung) demonstrating a neuroendocrine tumor. Although anecdotal, this may indicate that ^{18}F -DOPA still may have a role in detecting extra-pancreatic lesions of neuroendocrine cell origin in patient with vHL.

The basic concept of utilizing ^{18}F -DOPA in the detection of neuroendocrine tumors is the ability of these tumors to take up ^{18}F -dihydroxyphenylalanine and decarboxylate it by using aromatic amino acid decarboxylase (AADC), resulting in storage of ^{18}F -dopamine as secretory granules.^{15, 20} AADC is reported to be up-regulated in pheochromocytomas/paragangliomas, suggesting its potential utility to identify sub-clinical pheochromocytomas.²⁰ However, the expression of AADC appears to be extremely variable, especially among non-functioning PNETs,²¹ which may explain the variable ^{18}F -DOPA avidity in our study cohort.

One limitations of our study is that we used CT scan as the “gold-standard” for the detection of PNETs although it is known that the combination of different modalities usually provide the highest accuracy in the detection of PNETs.^{7, 9, 22} This may lead us to overestimate the accuracy of ¹⁸F-FDG and ¹⁸F-DOPA PET scans which was not as good as CT scan for detecting PNETs.

In conclusion, ¹⁸F-DOPA has very limited utility in detecting PNETs and metastatic PNETs in the setting of vHL. Although MRI and ¹⁸F-FDG did not identify all the PNETs identified by CT scans, they may identify additional PNETs and metastatic PNETs that were initially missed by CT scan. Multi-modal imaging using combination of CT, MRI, and ¹⁸F-FDG should be considered for the surveillance of PNETs in the setting of vHL. The utility of ¹⁸F-DOPA in identifying extra-pancreatic lesions in patients with vHL needs to be studies further in order to draw any conclusion.

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Figure 1.

Flow diagram indicating the breakdown of scans that were performed on the protocol and how many patients underwent evaluation by all 4 imaging modalities. There were total of 87 patients with vHL evaluated at the NIH from March 2010 to January 2011. 18 patients without evidence of PNETs were excluded from the analysis.

Figure 2.

Example of an ^{18}F -FDG and ^{18}F -DOPA avid lesion in the uncinate process of the pancreas from the same patient. (A) Scout image of the ^{18}F -FDG demonstrating an ^{18}F -FDG avid lesion in the area of the pancreas shown with a thick arrow, (B) ^{18}F -FDG avid lesion in the uncinate process in the cross-sectional image of the same ^{18}F -FDG shown with a SUV cursor, (C) Scout image of the ^{18}F -DOPA demonstrating an ^{18}F -DOPA avid lesion in the area of the pancreas shown with a thin arrow and a circle, (D) ^{18}F -DOPA avid lesion in the uncinate process in the cross-sectional image of the same ^{18}F -DOPA shown with a oval circle.

Table 1

Patient demographics

Patients with vHL screened from March 2010 to January 2011	
Patients	87
Patients with PNETs	69 (79%)
Male: Female	38:49
Mean/median age (years)	45.9±13/46 (range 16-73)
Average number of PNETs per patient based on CT scan	2.3
Mean/median size of PNETs identified on CT scan (cm)	1.3±0.91/1.1 (range 0.3-5.1)
Number of patients who underwent surgery	12

Table 2

Tumor detection by different modalities (n=40)

Imaging modality	No. of patients with positive lesions	No. of lesions identified	Sensitivity (%) [*]
CT	40	98	96
MRI	35	55	54
18F-FDG	28	45	44
18F-DOPA	8	11	11

* Based on total number of PNETs seen by CT, FDG and MRI.

Table 3

Patient characteristics who had avid PNETs on 18F-FDG or 18F-DOPA

A. 18F-FDG avid PNETs		B. 18F-DOPA avid PNETs	
Patients	44	Patients	9
Male: Female	17:27	Male: Female	3:6
Mean age (years)	45.7±13	Mean age (years)	52.9±10
No. of lesions identified	65	No. of lesions identified	12
Mean tumor size	1.8±0.97	Mean tumor size	1.5±0.54
Mean SUV	9.23±6.3	Mean SUV	8.06±5.58

Histological, chemical, and radiological features of resected PNETs

Table 4

Patient	Operative procedure	Size ¹	Location	18F-FDG avidity (SUV)	18F-DOPA avidity (SUV)	Serum chromogranin ²	Mitotic index (HPF)	MIB1 ³	Liver metastasis	LN metastasis	WHO classification ⁴
1	PD	1.7	Head	+(11)	-	119	0	low	-	+	1.1
2	EN	2.4	Head	+(12.6)	-	NA	2/10	5%	-	-	1.2
3	PD	1.7	Head	+(14)	-	130	low	NA	-	-	1.1
4	DP	4	Tail	+(15.6)	-	153	1/10	NA	+	+	1.1
5	DP	7	Body	+(8.1)	-	76	2/10	2%	-	+	1.2
6	DP	2.5	Body	+(17.2)	-	121	4/10	>2%	-	-	2
7	EN	2	Head	+(18.2)	+(10)	1105	Low	<2%	-	-	1.1
8	EN	3	Head	+(5.9)	+(27.9)	145	NA	2%	-	-	1.2
9	DP	2.5	Tail	-	-	129	low	low	-	-	5
10	TP	1.3	Head	-	-	326	NA	NA	-	-	1.2
11	PD	1.3	Head	+(12.8)	NA	142	2/10	>2%	-	-	1.2
12	DP	2	Body	+(4.0)	-	140	0	<1%	-	-	1.2

Abbreviations: PD, pancreaticoduodenectomy; EN, enucleation; DP, distal pancreatectomy; TP, total pancreatectomy; NA, not available; HPF, high-power field

¹ Size based on the greatest dimension on the final pathology

² All the values are in ng/ml. Value <= 225 ng/ml is considered normal

³ Immuno staining for proliferation marker is reported as MIB1 at the NIH as surrogate for Ki67

⁴ WHO histological classification of PNETs: 1, well-differentiated NET; 1.1, "benign" behavior; 1.2, Uncertain behavior; 2, Well-differentiated, low-grade malignant; 3, poorly differentiated malignant

⁵ Final pathology was microcytic cystadenoma