Published in final edited form as:

J Am Coll Surg. 2014 May ; 218(5): 997–1003. doi:10.1016/j.jamcollsurg.2014.01.004.

Prospective Evaluation of the Clinical Utility of 18-Fluorodeoxyglucose PET CT Scanning in Patients with Von Hippel-Lindau-associated Pancreatic Lesions

Samira M Sadowski, MD¹, Allison B Weisbrod, MD¹, Ryan Ellis, BS¹, Dhaval Patel, MD¹, Meghna Alimchandani, MD², Martha Quezado, MD², Corina Millo, MD³, David J Venzon, PhD⁴, Naris Nilubol, MD, FACS¹, W Marston Linehan, MD⁵, and Electron Kebebew, MD, FACS¹

¹Endocrine Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

²Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

³Positron Emission Tomography Department, National Cancer Institute, National Institutes of Health, Bethesda, MD

⁴Biostatistics and Data Management Section, National Cancer Institute, NIH, Bethesda, MD

⁵Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Abstract

Background—The natural history of pancreatic neuroendocrine neoplasms (PNEs) in patients with Von Hippel-Lindau (VHL) disease is poorly defined. Management of patients with PNEs is challenging because there are no reliable preoperative criteria to detect malignant lesions and the majority of resected tumors are found to be benign. The aim of this study was to determine whether 18-Fluorodeoxyglucose-Positron Emission Tomography (¹⁸FDG-PET) uptake predicts growth and detects malignant VHL-associated PNEs.

Study Design—Prospective study of 197 patients with VHL-associated pancreatic lesions. Clinical and imaging characteristics were analyzed to study the associations between FDG-PET uptake, tumor growth, and the development of metastatic disease.

Results—109 of 197 patients had solid pancreatic lesions and underwent both CT and ¹⁸FDG-PET scanning, which identified 165 and 144 lesions, respectively. ¹⁸FDG-PET detected metastatic disease in 3 patients not detected by CT scan and suggested non-neoplastic disease in 3 patients. Maximum SUV uptake on ¹⁸FDG-PET correlated with tumor size on CT ($r=0.47$, $p<0.0001$) and

Correspondence address: Samira M. Sadowski, MD, Endocrine Oncology Branch, National Cancer Institute, NIH Clinical Research Center, Building 10-CRC, Room 3W-5840, Bethesda, MD 20892. Phone: 301-451-1040 samira.sadowskiveuthey@nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure Information: Nothing to disclose.

an increase in SUV_{max} was associated with tumor growth ($r=0.36$, $p=0.0062$). No association was seen between ^{18}F FDG-PET uptake and age, *VHL* genotype, or serum chromogranin A levels.

Conclusions—FDG-PET scanning identifies metastatic disease not detected by CT scan and avoids the resection of non-PNEN lesions that have no malignant potential in patients with *VHL*-associated PNENs. It should be considered as a valuable functional imaging modality in the clinical management of patients with *VHL*-associated PNENs.

Keywords

Von Hippel-Lindau; Pancreatic neuroendocrine neoplasm; ^{18}F FDG-PET; metastatic

Introduction

Von Hippel-Lindau (*VHL*) disease is an autosomal dominant, multisystem familial cancer syndrome resulting from a germline inactivating mutation in the *VHL* tumor suppressor gene.¹ Patients with *VHL* are at risk of developing multiple benign and malignant tumors, including hemangioblastomas of the brain and spinal cord (10-70%), retinal hemangiomas (25-60%), endolymphatic sac neoplasms (10%), renal cysts and renal cell carcinomas (25-60%), pheochromocytomas (10-20%), and solid and cystic pancreatic neoplasms (35-70%).^{2, 3} Most pancreatic lesions are benign cysts, comprised of simple cysts or rarely serous cystadenomas.⁴ In contrast, solid lesions on CT scan are less common and usually indicate pancreatic neuroendocrine neoplasms (PNENs) (15% of *VHL* patients),^{3, 5} and may be malignant in up to 17% of patients.⁶

The primary goal in management of patients with *VHL*-associated pancreatic lesions is to prevent the development of metastatic disease while minimizing possible treatment related morbidity. And although there have been recent advances in medical therapies for metastatic PNENs, surgical resection remains the only curative therapy.⁷⁻⁹

Several imaging modalities have been used to detect PNENs. Computed tomography (CT) is the most widely used modality. The reported sensitivity of CT scan varies between 29-94%, with higher sensitivity achieved when both arterial and portal venous phases are performed.^{10, 11} This wide range of sensitivity is primarily due to small PNENs missed on CT. The combination of CT and MRI is able to localize >50% of PNENs larger than 3 cm, but only 5% of lesions smaller than 1 cm.¹² Recent studies suggest that functional imaging with positron emission tomography (PET) may be a useful localizing modality for PNENs. Radiolabeled 18-fluorodeoxyglucose (^{18}F -FDG) is taken up by some PNENs, especially poorly differentiated ones, and reflects increased glucose metabolism, which is linked to cellular proliferative activity and may be useful for distinguishing between benign and malignant lesions.^{13, 14} However, ^{18}F FDG-PET has been shown to be of limited utility for detecting well-differentiated tumors due to their low expression of glucose transporters and low proliferative activity.^{15, 16}

A widely used criterion for recommending surgical resection of *VHL*-associated PNENs is tumor size (> 3cm), however such an approach may miss some malignant tumors and may result in patients undergoing resection for a histologically benign tumor or non-PNEN.

Additional adjunct preoperative imaging studies, which could predict increased risk of disease progression or detect metastatic disease may refine the management of patients with VHL-associated pancreatic lesions. Thus, the aim of the present study was to determine prospectively whether the uptake status and amount of ^{18}F FDG-PET uptake could predict PNEN growth and detect malignant VHL-associated PNENs.

Methods

Patient Population

As part of a prospective clinical protocol, 197 patients with pancreatic manifestations of VHL were enrolled into a clinical protocol between June 2010 and December 2012 with serial axial imaging performed at the National Institutes of Health (NIH) Clinical Center (Clinicaltrials.gov: NCT00062166). All patients provided prior informed written consent and this study was approved by our Institutional Review Board.

Of the 197 patients followed in the study, 60 were excluded from this analysis because they presented with only pancreatic cysts. An additional 28 patients were excluded due to a lack of follow up imaging. This resulted in a study cohort of 109 patients with solid pancreatic lesions on CT scan. Clinical, demographic, laboratory, histopathologic and radiographic data were collected prospectively.

Imaging studies

As part of our clinical research protocol, patients with solid and complex lesions underwent pancreatic abdominal computed tomography (2mm slices, both arterial and portal venous phase) annually. ^{18}F FDG-PET scans were also performed annually for patients with solid lesions. The patients were required to fast for 4-6h before PET. Scans were performed 60 minutes after the administration of approximately 10 mCi of intravenous ^{18}F FDG for patients ≤ 90 kg and 15 mCi for patients >90 kg. Patients were scanned from the mid-thigh to the skull base. A non-contrast, non-diagnostic CT was used for attenuation and anatomic localization. Maximum standardized uptake values (SUV_{max}) were measured based on patient total body weight.

CT scans were assessed by two independent reviewers. The diagnosis of PNENs was made on the arterial phase of the CT. All solid radiographic lesions of the pancreas were catalogued by size and location. The largest diameter of each tumor was recorded by each reviewer and averaged to provide a consensus measurement. Average measurements less than 0.5 cm were excluded from the analysis.

Surgical management and histology

Patients who met the operative criteria at our institution underwent resection of their PNENs. Tumors were resected if they were ≥ 2 cm in the head of the pancreas or ≥ 3 cm in the body/tail of the pancreas. Twenty-four patients had a total of 29 lesions surgically removed. Lesions were classified by pathologists according to the 2010 World Health Organization (WHO) classification system for tumor grade, based on a combination of mitotic count and MIB1 (Ki67) labeling index as follows: Low grade (G1): <2 mitoses/10 hpf and $<3\%$ Ki67

index, Intermediate grade (G2): 2-20 mitoses/10hpf or 3%-20% Ki67 index, High grade (G3): >20 mitoses/10 hpf or >20% Ki67 index.

Statistical Analyses

Summary statistics are presented as mean $\pm$ standard deviation (SD), except where otherwise indicated. Associations between demographic, radiologic, clinicopathologic data and imaging results were evaluated using Spearman rank correlation coefficients, reported with 95% confidence intervals (CI) and exact permutation p values. Differences between groups in quantitative variables were assessed using the Mann-Whitney test. Due to within-patient correlation of SUV_{max} values over multiple lesions, associations with other lesion and patient characteristics were tested on a per patient basis from bootstrapped samples of one lesion per patient with median results reported to represent a typical sample. Statistical analyses were performed in GraphPad Prism, Version 5.04, 2010 (San Diego, California) and SAS/STAT software version 9.3 (copyright, SAS Institute Inc., Cary, NC).

Results

The study cohort demographics and clinical characteristics are summarized in **Table 1**. In 109 patients, CT detected 165 pancreatic solid lesions, and 144 of these were avid pancreatic lesions detected by ¹⁸FDG-PET. The average number of solid lesions per patient was thus 1.51 with a mean size of 1.50 cm by CT (median 1.30 cm, range 0.5-5.2 cm) and a mean SUV_{max} value of 7.5 (median 5.6, range 0-35.7).

The SUV_{max} significantly correlated with tumor size of the pancreatic lesion as measured by CT ($r=0.47$, 95% CI 0.41-0.54, $p<0.0001$, **Figure 1**). Of the 21 lesions that were not PET avid (SUV_{max} = 0), three had no contemporaneous CT size, and the average size of the other 18 was 1.22 ± 0.99 cm. The largest non-avid lesion measured 4.95 cm by CT and pathology revealed a 1.3 cm well-differentiated neuroendocrine tumor in association with a larger microcystic serous cystadenoma (MCA). Fifty-seven patients had 83 lesions with two or more ¹⁸FDG-PET scans and with tumor growth over the same time interval, in intervals ranging from 0.5 to 2.1 years (median 1.0) the change in SUV_{max} between these scans significantly correlated with the tumor growth ($r=0.36$, 95% CI 0.24-0.48, $p=0.0062$, **Figure 2**). However, the SUV_{max} at the initial ¹⁸FDG-PET scan was not found to be significantly associated with future tumor growth rate.

SUV_{max} was slightly higher in females than in males, with mean SUV_{max} values of 8.4 ± 6.6 for 62 females and 6.1 ± 5.4 for 47 males ($p=0.07$). Tumor size by CT was not significantly different by gender (1.46 cm in females versus 1.53 cm in males, median 1.30 in each). There was no association seen between SUV_{max} and age, genetic mutation (specific exon(s) involved) or serum chromogranin A levels (in 100 patients).

Twenty-four patients underwent resection of their PNENs during follow up. The operative intervention, pathology, and radiologic findings are summarized in **Table 2**. Average follow-up time after surgery was 36 months (median 37, range 19-51 months). Of the 24 patients, 22 had an ¹⁸FDG-PET scan prior to operative intervention, and CT scan demonstrated a total of 29 lesions. The majority of lesions (27/29) were avid on ¹⁸FDG-

PET, with a mean SUV_{max} of 10.3 ± 6.2 . There was no difference in SUV uptake seen by the histologic tumor grade (G1 versus G2) or nodal status (N0 versus N1). There was no difference in SUV_{max} seen in non metastatic versus metastatic PNENs (10.3 ± 6.7 and 10.5 ± 5.5). However, ^{18}F FDG-PET detected metastatic disease in 3 patients, which was not detected on CT scan. One patient had local invasion into the gastrohepatic ligament. The second patient was found to have retropancreatic lymph node involvement, and the third patient had a suspicious PET-avid peripancreatic lymph node that was metastatic PNEN on histologic examination. Representative images for the first patient are shown in **Figure 3**.

There was no ^{18}F FDG-PET uptake in two of 29 (6.9%) pancreatic lesions found on pathology, and both were small foci of PNEN (3 mm and 1.3 cm) with the large dominant lesion being MCA. A total of four patients presented with MCAs in addition to PNENs, and one had MCA only on final pathology. Of those, three had either no PNEN or concurrent small PNENs (3 mm to 1.3 cm). The comparison in SUV uptake between only PNENs and PNENs concurrent with MCA is shown in **Figure 4**. The SUV_{max} uptake was significantly lower in the group with MCA and concurrent PNENs ($p=0.0014$). Two lesions with high ^{18}F FDG-PET uptake in the combined PNEN and MCA group were PNEN of 6 cm of size on histologic examination. MCAs had a significantly lower ^{18}F FDG-PET SUV_{max} with none being above 4.2. For a total of 29 lesions with a histologic diagnosis, using a SUV_{max} cutoff of <4.0 versus >4.0 had a sensitivity of 92% (23/25), a specificity of 75% (3/4) and a positive and negative predictive value of 95.8% (23/24) and 60% (3/5), respectively, for detecting PNEN.

Discussion

To our knowledge this is the first prospective study evaluating the utility of ^{18}F FDG-PET in VHL-associated PNENs. Overall, ^{18}F FDG-PET localized 87% (144/165) of the solid pancreatic lesions (>0.5 cm) found on CT scan. The SUV_{max} by ^{18}F FDG-PET significantly correlated with lesion size by CT, but did not predict subsequent growth. However, we found increased SUV_{max} for those lesions that were larger on follow up imaging. Our results suggest a higher mean SUV_{max} in females compared to males, but we did not detect an association between ^{18}F FDG-PET uptake and age, genetic mutation status, or chromogranin A levels. ^{18}F FDG-PET identified 93% (27/29) of the tumors requiring surgical excision and helped identify metastatic lesions in 3 patients that were not seen by CT scan. MCAs had a significantly lower ^{18}F FDG-PET SUV_{max} with none being above 4.2, and overall the positive predictive value for ^{18}F FDG-PET in detecting PNEN was 95.8%.

In patients with PNENs, preoperative evaluation to determine the risk of malignancy or presence of metastatic disease is critical for determining the optimal treatment approach. CT scan has been traditionally used for this purpose, and studies have shown a correlation between tumor size and malignancy for sporadic nonfunctioning PNENs with a cutoff of >2 cm recommended for resection because of the higher risk of malignancy.¹⁷ Blansfield et al⁵ showed a similar size cutoff for VHL-associated PNENs. Because PNENs generally have an indolent course,¹⁸ we tested the idea of ^{18}F FDG-PET scanning possibly providing adjunct data to anatomic imaging studies that could optimize the management of patients with VHL-associated pancreatic lesions. Indeed, we found ^{18}F FDG-PET scanning was helpful for

distinguishing between PNENs and MCAs based on a SUV_{max} cutoff of 4.2. Because VHL-associated MCAs do not have a malignant potential they do not require operative intervention thus avoiding the potential morbidity of surgical treatment. We have implemented this finding in our protocol and only recommend surgical resection of complex or atypical enhancing pancreatic lesions on CT scan when the SUV_{max} is above 4.0. Our results also suggest that ^{18}F FDG-PET is useful in identifying metastatic disease missed by CT scan in patients with primary tumors which would have not fulfilled our size criteria for recommending surgical resection. Thus, ^{18}F FDG-PET allows for detection of metastatic disease and non-neoplastic pancreatic lesions in approximately 5% of patients with VHL, which has significant ramifications on their surgical management.

We found that PET avidity of VHL-associated PNENs was slightly higher in women. In non-small cell lung cancer, ^{18}F FDG-PET uptake has been shown to correlate negatively with survival in men when compared to women, with body composition not being a factor in the sex difference (lean body mass).¹⁹ These data suggest there may be a difference in tumor biology between sexes. In our study, the difference in ^{18}F FDG-PET SUV_{max} by sex could be confounded by body mass differences between sexes as we could not adjust for lean body mass. However, other investigators have shown body mass index (BMI) and gender influence mediastinal and liver ^{18}F FDG uptake, with lower uptake in men.²⁰

Several studies have shown ^{18}F FDG-PET to be promising as an alternative to tissue sampling for determining aggressiveness of tumors²¹ and to be of prognostic value in several other cancers including lung and head and neck cancers.^{22, 23} In patients with neuroendocrine neoplasms (NENs), investigators have shown that ^{18}F FDG-PET may be associated with tumors with high Ki67 indices.²⁴ Binderup et al²⁵ showed ^{18}F FDG-PET to be a predictor of progression-free survival in NENs when the SUV_{max} was >3.0 . However, our data did not show any association between PET avidity and WHO tumor grade, but the number of patients who required an operation was relatively small. We did not observe any association between ^{18}F FDG-PET avidity and exon 3 mutation or chromogranin A levels, both of which may be associated with metastatic or persistent/recurrent PNENs.^{5, 26, 27}

There are several limitations to the current study. First, CT was used as the “gold-standard” for the detection of PNENs in patients without pathologic confirmation in all cases. The combination of different modalities is known to provide the greatest accuracy in detection of PNENs,^{10, 11} and thus our results may overestimate the accuracy of ^{18}F FDG-PET in detecting PNENs. Our study was performed in patients with VHL-associated pancreatic lesions so may not be generalizable to other familial cancer syndromes such as MEN1 in which PNENs occur or in cases of sporadic PNENs. Our study also did not adjust for lean body mass when calculating SUV_{max} , which could have led to the finding of differential uptake by sex but this is not the default in clinical practice and thus our data is more applicable to the clinical setting most physicians obtain interpretations of ^{18}F FDG-PET scans. We do not routinely use endoscopic ultrasound with or without biopsy in patients with VHL-associated pancreatic lesions as most neuroendocrine tumors have typical features with arterial enhancement on CT scan and if the lesion is not a neuroendocrine tumor it is consistent with a cystadenoma which have no malignant potential in VHL. Moreover, the purpose of imaging studies in patients with VHL-associated pancreatic lesions is for follow up to detect

disease progression and or metastatic disease warranting an operation. We do perform endoscopic ultrasound with or without biopsy in special cases where patients have severe chronic kidney insufficiency as a result of multiple nephrectomies for renal cell carcinoma to avoid the risk of renal failure from intravenous contrast. Lastly, the 28 patients excluded from the cohort analyzed, for the lack of follow up imaging, had on average smaller tumors at enrollment. This may influence the observed association of SUV_{max} uptake and tumor size.

In conclusion, our data indicate that ¹⁸FDG-PET scanning should be considered a valuable adjunct test in the management of patients with VHL-associated PNENs. Semiquantitative SUV_{max} evaluation might give clinically valuable information as it accurately detects many of these lesions and identifies metastatic disease not seen by CT scan. More accurate identification of patient disease burden and better differentiation between nonmetastatic and metastatic lesions will improve treatment decision-making and avoid unnecessary treatment related morbidity.

Acknowledgments

Support: This research was supported by the intramural research program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health.

Abbreviations

CT	Computed Tomography
¹⁸FDG-PET	18-Fluorodeoxyglucose-Positron Emission Tomography
HPF	High power field
MCA	microcystic adenoma
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
NPV	Negative Predictive Value
PNENs	Pancreatic Neuroendocrine Neoplasms
PPV	Positive Predictive Value
VHL	Von Hippel-Lindau

References

1. Latif F, Tory K, Gnarr J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993; 260:1317–1320. [PubMed: 8493574]
2. Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. *Lancet*. 2003; 361:2059–2067. [PubMed: 12814730]
3. Charlesworth M, Verbeke CS, Falk GA, et al. Pancreatic lesions in von Hippel-Lindau disease? A systematic review and meta-synthesis of the literature. *J Gastrointest Surg*. 2012; 16:1422–1428. [PubMed: 22370733]

4. Mohr VH, Vortmeyer AO, Zhuang Z, et al. Histopathology and molecular genetics of multiple cysts and microcystic (serous) adenomas of the pancreas in von Hippel-Lindau patients. *Am J Pathol*. 2000; 157:1615–1621. [PubMed: 11073821]
5. Blansfield JA, Choyke L, Morita SY, et al. Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). *Surgery*. 2007; 142:814–818. discussion 818 e1-2. [PubMed: 18063061]
6. Corcos O, Couvelard A, Giraud S, et al. Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological, and genetic features. *Pancreas*. 2008; 37:85–93. [PubMed: 18580449]
7. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology*. 2008; 135:1469–1492. [PubMed: 18703061]
8. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011; 364:501–513. [PubMed: 21306237]
9. Ehehalt F, Saeger HD, Schmidt CM, Grutzmann R. Neuroendocrine tumors of the pancreas. *Oncologist*. 2009; 14:456–467. [PubMed: 19411317]
10. Noone TC, Hosey J, Firat Z, Semelka RC. Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. *Best Pract Res Clin Endocrinol Metab*. 2005; 19:195–211. [PubMed: 15763695]
11. Rockall AG, Reznick RH. Imaging of neuroendocrine tumours (CT/MR/US). *Best Pract Res Clin Endocrinol Metab*. 2007; 21:43–68. [PubMed: 17382265]
12. Oberg K. Pancreatic endocrine tumors. *Semin Oncol*. 2010; 37:594–618. [PubMed: 21167379]
13. Binderup T, Knigge U, Loft A, et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. *J Nucl Med*. 2010; 51:704–712. [PubMed: 20395333]
14. Tatsumi M, Isohashi K, Onishi H, et al. 18F-FDG PET/MRI fusion in characterizing pancreatic tumors: comparison to PET/CT. *Int J Clin Oncol*. 2011; 16:408–415. [PubMed: 21347626]
15. Eriksson B, Orlefors H, Oberg K, et al. Developments in PET for the detection of endocrine tumours. *Best Pract Res Clin Endocrinol Metab*. 2005; 19:311–324. [PubMed: 15763703]
16. Adams S, Baum R, Rink T, et al. Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. *Eur J Nucl Med*. 1998; 25:79–83. [PubMed: 9396878]
17. Bettini R, Partelli S, Boninsegna L, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery*. 2011; 150:75–82. [PubMed: 21683859]
18. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010; 39:707–712. [PubMed: 20664470]
19. Wainer Z, Daniels MG, Callahan J, et al. Sex and SUVmax: sex-dependent prognostication in early non-small cell lung cancer. *J Nucl Med*. 2012; 53:1676–1685. [PubMed: 22984219]
20. Malladi A, Viner M, Jackson T, et al. PET/CT mediastinal and liver FDG uptake: Effects of biological and procedural factors. *J Med Imag Radiat Oncol*. 2013; 57:169–175.
21. Vesselle H, Schmidt RA, Pugsley JM, et al. Lung cancer proliferation correlates with [F-18]fluorodeoxyglucose uptake by positron emission tomography. *Clin Cancer Res*. 2000; 6:3837–3844. [PubMed: 11051227]
22. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med*. 2000; 343:254–261. [PubMed: 10911007]
23. Torizuka T, Tanizaki Y, Kanno T, et al. Prognostic value of 18F-FDG PET in patients with head and neck squamous cell cancer. *AJR*. 2009; 192:W156–160. [PubMed: 19304675]
24. Pasquali C, Rubello D, Sperti C, et al. Neuroendocrine tumor imaging: can 18F-fluorodeoxyglucose positron emission tomography detect tumors with poor prognosis and aggressive behavior? *World J Surg*. 1998; 22:588–592. [PubMed: 9597933]
25. Binderup T, Knigge U, Loft A, et al. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res*. 2010; 16:978–985. [PubMed: 20103666]

26. Bajetta E, Ferrari L, Martinetti A, et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. *Cancer*. 1999; 86:858–865. [PubMed: 10463986]
27. Nykjaer KM, Gronbaek H, Nielsen DT, et al. Description of patients with midgut carcinoid tumours: clinical database from a Danish centre. *In Vivo*. 2007; 21:679–684. [PubMed: 17708366]
28. Bilimoria KY, Bentrem DJ, Merkow RP, et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. *J Am Coll Surg*. 2007; 205:558–563. [PubMed: 17903729]
29. Edge, S.; Labow, D.; Carduci, M. *AJCC Cancer Staging Manual*. 7th ed.. Springer; New York, NY: 2010.
30. Bosman, F.; Carneiro, F.; Hruban, R.; Theise, N. *WHO Classification of Tumors of the Digestive System*. 4th ed. International Agency for Research on Cancer; Lyon, France: 2010.

Precis

18-Fluorodeoxyglucose-PET improves detection of metastatic disease and non-neoplastic disease in patients with Von Hippel-Lindau -associated pancreatic lesions.

Figure 1.

Association between ^{18}F FDG-PET uptake and the size of the pancreatic lesion on CT, measured at same time point, N=156. Spearman correlation $r= 0.47$, 95% CI 0.41-0.54, $p<0.0001$. SUV_{max} = Maximum standardized uptake value.

Figure 2.

Association between the change in ^{18}F FDG-PET uptake and growth of solid pancreatic lesion in cm over the same time period, N=83. Spearman correlation $r=0.36$, 95% CI 0.24-0.48, $p=0.0062$. SUV_{max} = Maximum standardized uptake value.

Figure 3.

Representative case of a 44 year-old man with metastatic PNEN. The patient had pancreatic extension into the gastrohepatic ligament seen on ^{18}F FDG-PET and was found to have liver metastases. Images A and B show the ^{18}F FDG-PET with the body mass of SUV_{max} 15.6 (B, arrow) and its suspicious extension into the gastrohepatic ligament (A, arrow). Images C demonstrates absence of the lesion shown in image A and D show the CT scan of the pancreatic body mass of 4cm (D, arrow).

Figure 4.

Comparison of preoperative SUV_{max} according to final pathology (per lesion analysis). Mann-Whitney test, **p=0.0014. MCA, microcystic adenoma; PNEN, pancreatic neuroendocrine neoplasms; PreOP SUV_{max}, preoperative maximum standardized uptake value.

Table 1

Characteristics of Study Cohort

Variable	Value
n	197
Pts with solid PNEN, n (%)	137 (69.5)
Pts with CT and FDG-PET	109
Male : female ratio	47 : 62
Median age, y (range)	47 (18-74)
No. of lesions on CT / PET	165 / 144
Average no. of PNENs per patient (range)	165/109= 1.51 (1-4)
Size of PNENs on CT, cm, mean $\pm$ SD (range)	1.50 $\pm$ 0.88 (0.5-5.2) n=165
SUV _{max} on PET, mean $\pm$ SD (range)	7.5 $\pm$ 6.2 (0-35.7) n=144
Median chromogranin a, ng/mL (range)	150 (32-3,560) n=100
Patients who underwent resection, n	24

PNENs, pancreatic neuroendocrine neoplasms.

Table 2

Histologic and Radiologic Features of Resected pancreatic Neuroendocrine Neoplasms in 24 Patients with Von Hippel-Lindau

	All patients	Patients with MCAs+concurrent PNENs (n=5 [¶])	PNENs only (n=19)
Patients with resection for solid tumors; n (% of resected)	24 (100)	5 (20.8)	19 (79.2)
Age at operation, y, median (range)	47 (24-71)	48 (33-56)	47 (24-71)
Resection performed, n [*]	25	6	19
Total pancreatectomy	3	1	2
Pancreaticoduodenectomy	7	1	6
Distal pancreatectomy	8	3	5
Enucleation	7	1	6
FDG-PET uptake; mean $\pm$ SD (range)	10.3 $\pm$ 6.2 (0-25)	4.5 $\pm$ 4.0 (0-10.4)	12.2 $\pm$ 5.7 (3.5-25) [†]
Size of tumor lesion, cm, mean $\pm$ SD (range) [‡]	2.30 $\pm$ 1.51 (0-7)	1.72 $\pm$ 2.22 (0-6)	2.45 $\pm$ 1.29 (1.3-7)
PNEN staging; n/no. evaluable (% of group) [§]			
T1, $\leq$ 2 cm		3/4 (75)	7/19 (37)
T2, limited to pancreas $>$ 2 cm		1/4 (25)	10/19 (53)
T3, beyond pancreas, no involvement of SMA and celiac		0	2/19 (11%)
T4, beyond pancreas with involvement of SMA and celiac			
N1		1/5(20)	6/19(32)
M1; n (%)		0	2/19(11)
Grade, n (%)			
1		2/4 (50)	11/19 (58)
2		2/4 (50)	8/19 (42)

* One patient had more than one procedure performed, thus the number of resections is greater than the number of patients.

[†] n=17.

[‡] Largest PNEN size on final pathology.

[§] TNM stage according to the American Joint Committee on Cancer^{28, 29} and the World Health Organization histologic classification for PNEN (1 low grade NEN; 2 intermediate NEN; 3 high grade NEC).³⁰

[¶] Overall 5 patients with MCAs, 1 patient MCA only, 4 concurrent MCA+PNENs FDG, 18-Fluorodeoxyglucose; PNENs, pancreatic neuroendocrine neoplasms; SMA, superior mesenteric artery; VHL, Von Hippel-Lindau.