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Research article

The utility of ^{68}Gallium-DOTATATE PET/CT in the detection of von Hippel-Lindau disease associated tumors

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ABSTRACT

Purpose: Patients with von Hippel-Lindau (VHL) disease may develop various tumors, including neuroendocrine tumors of the pancreas (PNETs) and adrenal, central nervous system and retinal hemangioblastomas, kidney tumors and more. ^{68}Ga-DOTATATE positron emission tomography (PET)/computerized tomography (CT) has been shown to be highly accurate for tumors with cells expressing somatostatin receptors. We aimed to assess the performance of ^{68}Ga-DOTATATE PET/CT in patients with VHL disease.

Methods: Patients with a diagnosis of VHL were enrolled in a prospective study and underwent surveillance imaging for pancreatic lesions (n = 301). The current analysis includes 73 evaluations with multiple imaging modalities of 36 patients (2.1 ± 0.8 evaluations/patient, range 1–4) for a head-to-head comparison of ^{68}Ga-DOTATATE PET/CT, CT and/or MRI. In this post-hoc analysis we compared the detection rates of various imaging modalities for PNETs and for any extrapancreatic tumors located within the scan field of CT/MRI of the abdomen.

Results: ^{68}Ga-DOTATATE PET/CT detected a total of 206 lesions, CT detected 208 lesions and MRI detected 94 lesions in 61, 66 and 33 scans, respectively. ^{68}Ga-DOTATATE PET/CT (3.4 ± 0.1 per scan) was superior than CT (3.2 ± 0.1 per scan, p = 0.02) with a similar trend when comparing with MRI (2.8 ± 0.1 per scan, p = 0.03) in detecting lesions in any anatomic locations.

Conclusions: ^{68}Ga-DOTATATE PET/CT had a significantly higher detection rate when compared with anatomic imaging for all lesions, and comparable detection rate for pancreatic lesions in VHL patients. Hence, given the higher accuracy and lower radiation exposure associated with ^{68}Ga-DOTATATE PET/CT, its potential role in the surveillance of VHL-associated lesions should be further studied.

1. Introduction

Von Hippel-Lindau (VHL) disease is an autosomal dominant syndrome characterized by benign and malignant solid lesions as well as cystic lesions which develop in a variety of organ systems [1]. VHL is caused by a germline mutation in the *VHL* gene and has an incidence of one in 36,000 live births, with a 90% penetrance by the age of 65 [1,2]. The *VHL* gene is a tumor suppressor gene located on chromosome 3p25-26 [1]. Active surveillance of patients with VHL leads to earlier diagnosis and lower morbidity and mortality from renal cell carcinoma and central nervous system hemangioblastomas [1,3]. Other manifestations of VHL include renal cysts, pheochromocytomas, pancreatic tumors and cysts, and epididymal cystadenomas [1,3].

PNETs are present in 8–17% of patients with VHL, with a mean age at presentation of 35 years for solid lesions and a mean age of 37 years for cystic lesions [1,4]. The lesions are generally nonfunctional,

Abbreviations: VHL, Von Hippel-Lindau; PNET, pancreatic neuroendocrine tumor; CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; ^{68}Ga-DOTATATE, ^{68}Galium- DOTA^{0}-Tyr^{3}–octreotate; ^{18}F-FDG, ^{18}F-2-Deoxy-d-glucose

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multifocal and distributed throughout the pancreas [4]. VHL-associated PNETs have an overall good prognosis, however, 10–20% may develop lymph node or distant metastasis, and would, therefore, be classified as malignant [4,5].

Risk factors for malignant VHL-associated PNETs include missense and/or exon 3 mutation, a tumor size greater than 3 cm, in addition to short tumor diameter doubling time, and other genetic markers [6–9]. However, in the case of VHL-associated PNETs, imaging becomes an integral part of patient screening and surveillance. Surgical resection is indicated if there is a lesion greater than 2 cm in the head of the pancreas or 3 cm elsewhere, and if metastases are present that can be resected [6,9,10].

Imaging modalities commonly used for the screening and surveillance for VHL-associated PNETs include computed tomography (CT) and magnetic resonance imaging (MRI). CT scanning has a sensitivity of 30–80% depending on the size of the tumor and quality and protocol of the imaging study [11,12]. MRI is less accurate for detecting PNETs but is complementary to CT, especially in cases where there are liver metastases [11]. ^{18}F-2-Deoxy-D-glucose PET/CT (^{18}F-FDG) may be useful in identifying metastasis and distinguishing PNETs from other VHL-associated pancreatic lesions [13,14].

^{68}Gallium [68Ga]-DOTA peptide (DOTATATE, DOTANOC, DOTATOC) PET/CT is a functional imaging modality that takes advantage of the high somatostatin receptors (SSTR) expression in neuroendocrine cells [15]. ^{68}Ga-DOTATATE PET/CT has been shown to be over 80% sensitive and 90% specific for detecting NETs, which has made it useful for managing patients with PNETs [16–21]. Moreover, ^{68}Ga-DOTATOC PET/CT was studied for the surveillance of VHL-related PNETs in a small group of patients, and was found more sensitive compared with CT and MRI [22].

Interestingly, there are cumulative evidence on the detection of various VHL associated tumors, in addition to PNETs, by ^{68}Ga-DOTATATE PET/CT [23–26]. This is important, as it can reduce the burden on the patients both in terms of time, and radiation exposure, and utilize a single whole body, low-radiation scan, to detect lesions in this multi-neoplasm disease. In addition, considering the limited data on the role of ^{68}Ga-DOTATATE PET/CT imaging in patients with VHL-associated PNETs, we aimed to determine the clinical accuracy of ^{68}Ga-DOTATATE PET/CT in patients with VHL-associated pancreatic lesions, comparing with anatomic imaging modalities.

2. Material and methods

2.1. Patient selection

Patients with a diagnosis of VHL-associated pancreatic lesion(s) were enrolled in a natural history protocol at the National Institutes of Health Clinical Center (NCT00062166) approved by the institutional IRB, after written informed consent. The surveillance of pancreatic lesions was done using contrast-enhanced CT scans. Thirty-six of 301 patients enrolled had concurrent ^{68}Ga-DOTATATE PET/CT and anatomic imaging (CT and/or MRI) for a head-to-head comparison of their detection rates. All patients had annual imaging follow-up for solid pancreatic lesions and every 2 years for pancreatic cystic lesions.

2.2. Imaging evaluation

Five mCi (± 10%) of ^{68}Ga-DOTATATE was administered through a peripheral vein. After approximately 60 min, the patient was positioned supinely in a PET/CT scanner (Siemens Medical Solutions USA, Inc.), and images from the upper thighs to mid-skull were obtained. A non-contrast CT was used for attenuation correction and anatomic localization. Maximum standardized uptake values (SUV_{max}) were measured based on patient total body weight. All patients also had anatomic imaging with chest, abdomen and pelvis CT scan using LightSpeed Ultra, LightSpeed QX/i (General Electric Healthcare Technologies, Waukesha, WI), and Mx8000 IDT (Philips Medical Systems, Andover, MA) scanners (arterial and portal venous phase, 2 mm slices, with a rapid infusion of nonionic water-soluble contrast agent [130 mL injected at 2 mL/s], as well as oral contrast).

Abdominal and pelvic MRI was performed, to include T2 series with and without fat saturation and short tau inversion recovery and T1 pre- and postcontrast series, after intravenous injection of gadoliniumdiethylentriamine pentaacetic acid (Siemens Verio 1.5 T; Siemens Medical Solution, Malvern, PA; and Philips Achieva 1.5 and 3 T; Philips Medical Systems). CT scanning and MRI were performed within 1 week of ^{68}Ga-DOTATATE PET/CT scanning.

The comparisons between ^{68}Ga-DOTATATE PET/CT and anatomic imaging modalities included only lesions that could be located within the scan field of all three modalities, including the lung bases superiorly and the pelvic inferiorly. Hence, lesions in the cerebellum and in the upper thoracic or cervical spine were reported in the total lesions detected by ^{68}Ga-DOTATATE PET/CT, but were not included in the comparisons with CT and MRI. In addition, since it is not possible to determine with certainty whether a lesion is a primary tumor or metastasis, we grouped the tumors into pancreatic lesions, and extra-pancreatic lesions, with the aim of comparing the detection rate of the ^{68}Ga-DOTATATE PET/CT vs. CT/MRI for PNETs specifically, and for VHL-associated lesions in general. Radiologists and nuclear medicine physicians reviewed images in a blinded fashion. Non-physiologic uptake on ^{68}Ga-DOTATATE PET/CT imaging were considered true positive lesions.

2.3. Statistical analysis

Statistical analyses were performed using GraphPad Prism 7 software (GraphPad Software, La Jolla, CA) and SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

The detection rates of CT, MRI and ^{68}Ga-DOTATATE PET/CT were compared using the paired t-test, unless mentioned otherwise, to detect the difference in detection rates between the various modalities per evaluation in the same patients. Continuous variables were compared by Student's t-test, and categorical variables by Chi-squared test. Non-parametric tests were used as appropriate. Data are presented as mean ± standard deviation (SD), unless otherwise indicated. To correct for multiple comparisons (^{68}Ga-DOTATATE vs. CT and vs. MRI), a two-tailed p value < 0.025 was considered statistically significant.

3. Results

The study cohort demographics, clinical characteristics and biochemical profiles are summarized in Table 1. The current analysis included 36 patients who had 73 evaluations (mean 2.1 ± 0.8 evaluations per patient, range 1–4). The mean age was 46.3 ± 11.0 years and

Table 1
Demographic, clinical characteristics and biochemical data of study cohort.

Clinical Characteristics and Manifestations of Cohort	
Variable	Patients with VHL (n = 36)
Female n (%)	21 (58.3%)
Age, mean ± SD	46.3 ± 11.0
Extra-pancreatic VHL manifestation, n (%)	
Renal cell carcinoma	14 (38.9%)
Retinal angioma	10 (27.8%)
Hemangioblastoma	23 (63.9%)
Pheochromocytoma	10 (27.8%)
Endolymphatic sac tumors	2 (5.6%)
Patients who underwent operative intervention after ^{68}Ga-DOTATATE PET/CT, n (%)	12 (33%)

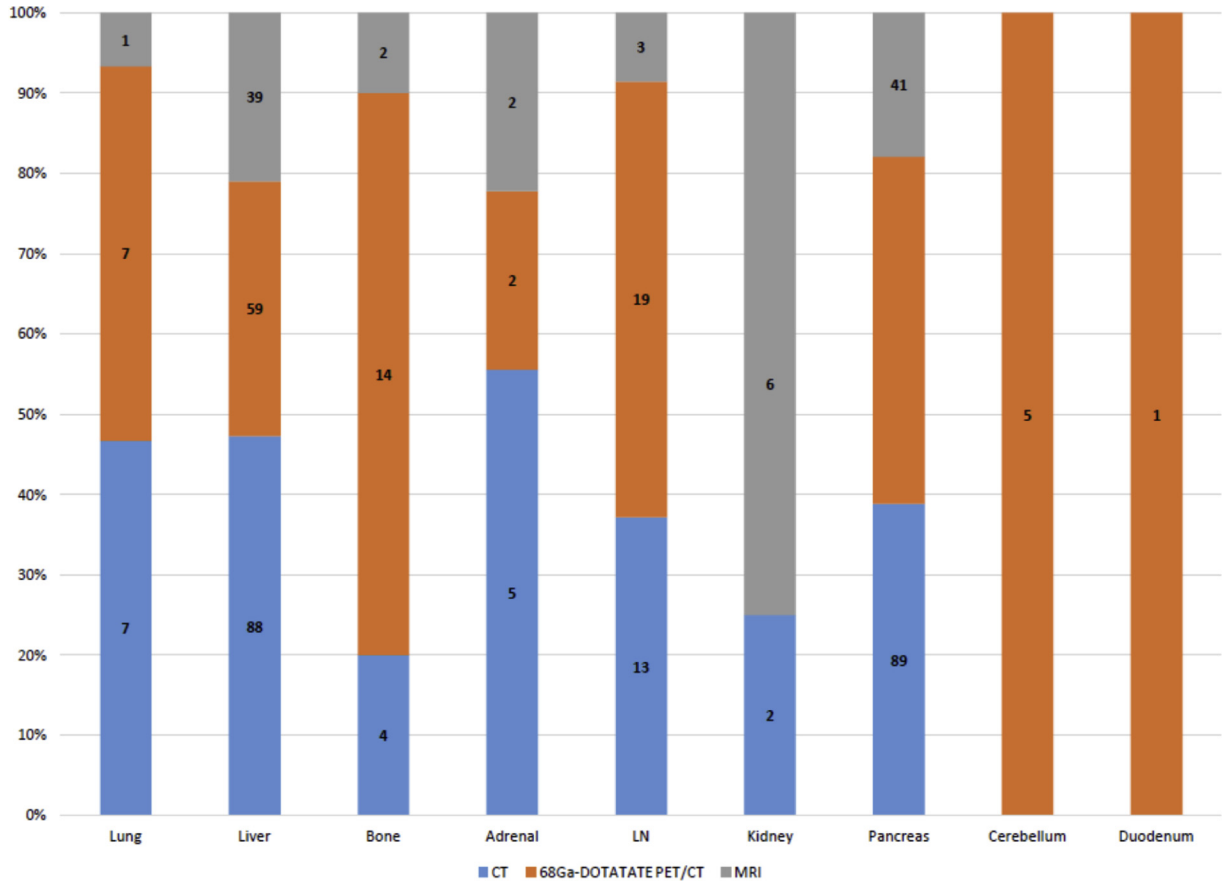

Fig. 1. Anatomic locations of lesions detected by different imaging modalities in patients with von Hippel-Lindau disease.
CT, computerized tomography; MRI, magnetic resonance imaging; LN, lymph node(s).

Table 2
Difference in number of lesions detected in a single visit between different imaging modalities, of pancreatic and extra-pancreatic lesions.

	CT vs. MRI (n = 27)	CT vs. DOTATATE (n = 55)	MRI vs. DOTATATE (n = 31)
Total lesions	0.07 ± 0.3 (p = 0.8)	−0.7 ± 0.3 (p = 0.02)	−1.5 ± 0.6 (p = 0.03)
Pancreatic	0 ± 0.2 (p = 1.0)	−0.2 ± 0.2 (p = 0.085[a])	−0.2 ± 0.2 (p = 0.4)
Extra-pancreatic	0.2 ± 0.4 (p = 0.6)	−0.4 ± 0.2 (p = 0.07)	−1.3 ± 0.5 (p = 0.045)

Numbers represent mean ± standard deviation of the n lesions detected by 1st – 2nd imaging modalities in each column. CT, computerized tomography; MRI, magnetic resonance imaging; DOTATATE, ^{68}Ga-DOTATATE positron emission tomography (PET)/CT.
[a] Mann-Whitney U test.

21 (58.3%) patients were female. Of the 36 patients, 13 (36.1%) had surgical resection of their tumor. A total of 208 lesion were detected by CT in 66 scans (89 pancreatic and 119 extra-pancreatic), 94 lesions were detected by MRI in 33 scans (41 pancreatic and 53 extra-pancreatic) and 206 by ^{68}Ga-DOTATATE PET/CT in 61 scans (99 pancreatic and 107 extra-pancreatic, Fig. 1). Paired comparisons of the number of lesions detected per evaluation between different modalities show a higher number of lesions detected per scan by ^{68}Ga-DOTATATE PET/CT in any anatomic location (p = 0.02 and p = 0.03 for comparisons with CT and MRI, respectively), and a trend of higher number of pancreatic lesions detected compared with CT (p = 0.085, Mann-Whitney U test), and of extra-pancreatic lesions detected compared with CT (p = 0.07) or MRI (p = 0.045, Table 2).

There were 24 lesions not seen by CT or MRI which were detected by ^{68}Ga-DOTATATE PET/CT. In 14 patients (37.8%) additional extra-pancreatic lesions were detected by ^{68}Ga-DOTATATE PET/CT as compared to CT or MRI. The lesions detected only on ^{68}Ga-DOTATATE PET/CT included retroperitoneal lymph nodes, liver lesions, lumbar spine hemangioblastomas and lesions in the lung bases parenchyma (Figs. 2 and 3).

4. Discussion

In this study, we compared the clinical utility of ^{68}Ga-DOTATATE PET/CT in detecting PNETs in VHL patients, as well as additional other VHL-associated lesions as compared with current recommended imaging modalities of CT/MRI. We found that ^{68}Ga-DOTATATE PET/CT detected more lesions per evaluation, compared with both CT and MRI.

CT scan of the abdomen and pelvis ith and without contrast, the protocol required for VHL-related lesion detection, is associated with a higher radiation exposure than ^{68}Ga-DOTATATE PET/CT (Table 3) [27,28]. This suggests that ^{68}Ga-DOTATATE PET/CT imaging for screening and surveillance of VHL-associated PNETs may be preferable. An additional advantage of ^{68}Ga-DOTATATE PET/CT is that it is not nephrotoxic unlike intravenous contrast agents used for CT scanning and this is important in patients with VHL as many patients may have chronic renal insufficiency from previous nephrectomies for renal cell carcinoma. As the VHL population is already at risk for renal failure and

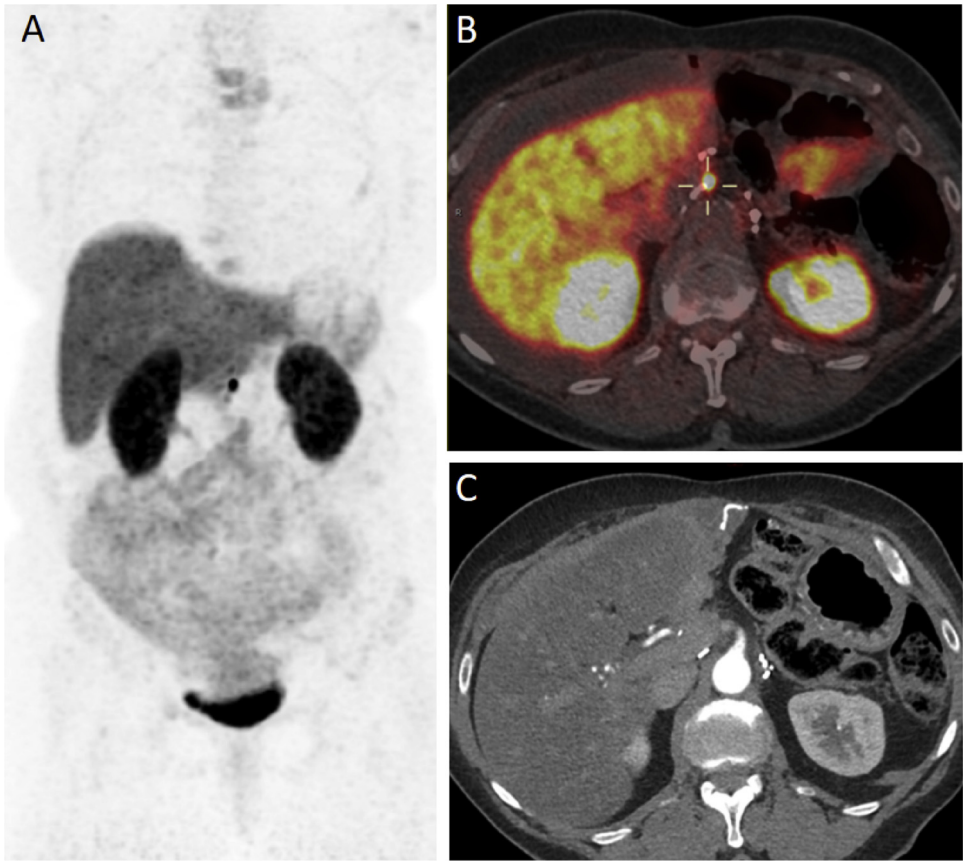

Fig. 2. Extra-pancreatic lesion, suspected as a recurrence of pancreatic neuroendocrine tumor in a previous surgery bed, detected by ^{68}Ga-DOTATATE PET/CT, but not by CT scan. (A) Coronal maximal intensity projection (MIP), and transverse image of ^{68}Ga-DOTATATE PET/CT (A & B) demonstrating a lesion very clearly, and a transverse view of early arterial phase of CT scan, not demonstrating the lesion.
CT, computerized tomography; PET, positron emission tomography.

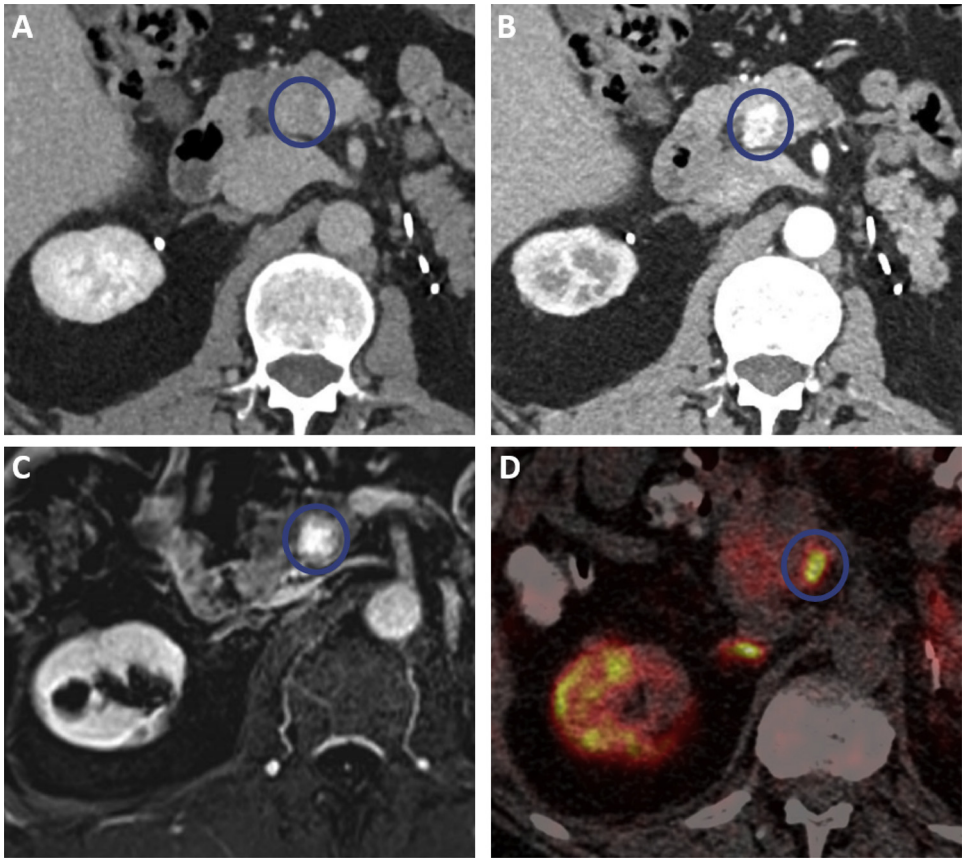

Fig. 3. Typical appearances of pancreatic neuroendocrine tumors in patients with VHL in various imaging modalities: non-contrast computerized tomography (CT, A), arterial phase of contrast enhanced CT (B), magnetic resonance imaging T2 phase after injection of gadolinium (C) and ^{68}Ga-DOTATATE PET/CT fusion image (D).

Table 3
Radiation dose comparisons by imaging modality [27,28].

Imaging modality	Radiation dose (mSv)
CT Chest, without contrast	8
CT Chest, with contrast	8
CT Abdomen and Pelvis, without contrast	15
CT Abdomen and Pelvis, with contrast	16
CT Chest, Abdomen and Pelvis, with contrast	24
^{18}F-FDG PET/CT	7
^{68}Ga-DOTATATE PET/CT	5

CT, computerized tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

dialysis, any additional protective measures that avoid risk factors for renal failure would be of great benefit.

^{68}Ga-DOTATATE PET/MRI is a novel imaging modality, combining whole body MRI with ^{68}Ga-DOTATATE PET. Our study protocol did not include this imaging modality and thus we could not report its relative accuracy. However, the superiority of ^{68}Ga-DOTATATE PET/MRI over ^{68}Ga-DOTATATE PET/CT in the detection of neuroendocrine tumors was previously reported [29]. Moreover, a fast non-enhanced sequence of ^{68}Ga-DOTATATE PET/MRI was studied in patients with renal failure and found comparable to PET/CT [30], a topic of high relevance in surveillance of patients with VHL. Considering the high accuracy of MRI in soft tissues in general and particularly in the central nervous system, and the sensitivity of ^{68}Ga-DOTATATE PET for VHL-related lesions, PET/MRI has a high potential to be useful for screening of VHL-related visceral neoplasms.

The possible impact of using ^{68}Ga-DOTATATE PET/CT for screening of VHL patients for visceral lesions may lead to early detection of such lesions, and early identification of fast-growing neoplasms with an appropriate intervention. On the other hand, the high sensitivity of ^{68}Ga-DOTATATE PET/CT will lead to higher number of lesions detected, which should be interpreted cautiously, as these will not represent disease of higher risk. Moreover, one clinical situation that should be addressed is the detection of a lesion by ^{68}Ga-DOTATATE PET/CT, that is not confirmed by anatomic imaging modality. Although ^{68}Ga-DOTATATE PET/CT has higher sensitivity compared with CT or MRI for neuroendocrine tumors, it does have physiological uptake that may lead to false positive findings. Thus, each ^{68}Ga—DOTATATE-positive lesion that is not demonstrated by CT or MRI should be interpreted in the context of its anatomical location, and if required, repeated CT or MRI in a short time interval may be required.

The use of ^{68}Ga-DOTATATE PET/CT is well established in European countries, and was approved by the United States Food and Drug Agency (FDA) in June 2016, leading to increased availability of this imaging modality. However, even when available, the required radiotracer and the PET scan itself, constitute additive costs that should be considered before recommending it for routine use.

The current study has several limitations. First, the study cohort may be too small to detect a small difference in detection rate resulting in a type II statistical error, but VHL-associated PNETs are not common. Second, histologic examination was not available for all lesions detected as not all patients required an operation, hence we could not analyze metastatic PNET separately from other visceral tumors. Third, the main modality used for the detection and surveillance of PNETs in the current population was CT scan. This may have led to biased sensitivity calculations, and may explain the lack of difference in pancreatic lesions detection-rates by falsely increasing the sensitivity of CT compared with other modalities.

5. Conclusions

^{68}Ga-DOTATATE PET/CT has a higher detection rate for VHL-associated lesions when compared to CT and MRI. There was no significant difference in the number of lesions detected between the imaging modalities for solid VHL-associated pancreatic lesions. Given that ^{68}Ga-DOTATATE PET/CT has lower radiation exposure than CT scan, it would be a reasonable choice for screening and surveillance of VHL-associated tumors.

Disclosure summary

The authors certify that they have no competing interests

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