Comparison of Diagnostic Sensitivity and Quantitative Indices Between ^{68}Ga -DOTATOC PET/CT and ^{111}In -Pentetreotide SPECT/CT in Neuroendocrine Tumors: a Preliminary Report

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Abstract

Purpose In-pentetreotide has been used for neuroendocrine tumors expressing somatostatin receptors. Recently, ^{68}Ga -DOTATOC PET has been used with the advantage of high image quality. In this study, we compared quantitative indices between ^{111}In -pentetreotide SPECT/CT and ^{68}Ga -DOTATOC PET/CT.

Methods Thirteen patients diagnosed with neuroendocrine tumors were prospectively recruited. Patients underwent ^{111}In -pentetreotide scans with SPECT/CT and ^{68}Ga -DOTATOC PET/CT before treatment. The number and location of lesions were analyzed on both imaging techniques to compare lesion detectability. Additionally, the maximal uptake count of each lesion and mean uptake count of the lungs were measured on both imagings, and target-to-normal lung ratios (TNR) were calculated as quantitative indices.

Results Among 13 patients, 10 exhibited lesions with increased uptake on ^{111}In -pentetreotide SPECT/CT and/or ^{68}Ga -DOTATOC PET/CT. Scans with SPECT/CT detected 19 lesions, all of which were also detected on PET/CT.

Moreover, 16 additional lesions were detected on PET/CT (6 in the liver, 9 in the pancreas and 1 in the spleen). PET/CT exhibited a significantly higher sensitivity than SPECT/CT (100 % vs. 54 %, $P<0.001$). TNR was significantly higher on PET/CT than on SPECT/CT (99.9 ± 84.3 vs. 71.1 ± 114.9 , $P<0.001$) in spite of a significant correlation ($r=0.692$, $P=0.01$).

Conclusion ^{68}Ga -DOTATOC PET/CT has a higher diagnostic sensitivity than ^{111}In -pentetreotide scans with SPECT/CT. The TNR on PET/CT is higher than that of SPECT/CT, which also suggests the higher sensitivity of PET/CT. ^{111}In -pentetreotide SPECT/CT should be used carefully if it is used instead of ^{68}Ga -DOTATOC PET/CT.

Keywords Neuroendocrine tumors · ^{68}Ga -DOTATOC · ^{111}In -pentetreotide · Positron emission tomography · Single-photon emission-computed tomography

Introduction

Neuroendocrine tumor (NET) is a heterogeneous group of malignant tumors that originate from the diffuse neuroendocrine system [1, 2]. The most common origins of NET are the gastrointestinal tract and bronchopulmonary system [3]. Although the absolute incidence of NET is very low, the incidence increased five-fold from 1973 to 2004 [4].

For diagnosis of NETs, conventional radiological imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) have been used [5, 6]. However, these anatomical imaging methods exhibit limited diagnostic value if the lesions are small and scattered or the anatomical structure has been altered after surgery [5]. Thus, molecular imaging has been applied to diagnose NET, particularly targeting somatostatin receptors

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(SSTR). In the majority of NETs, SSTR is overexpressed on the cell surface [2, 7], and SSTR 2 is the most abundant of the five subtypes [8]. Therefore, radiolabeled somatostatin analogs can be used for the diagnosis and treatment of NETs [2, 9].

^{111}In -DTPA-octreotide has long been used for SSTR scintigraphy, which is regarded as a standard imaging method for diagnosing NET [2, 5]. Recently, hybrid imaging of single-photon emission computed tomography (SPECT)/CT has been available, which enables anatomical localization and attenuation correction of SPECT images [5]. In addition to ^{111}In -DTPA-octreotide imaging, positron emission tomography (PET) has also been used for diagnosing NETs. PET exhibits higher spatial resolution and sensitivity [7] than planar scans or SPECT. PET using ^{68}Ga -labeled somatostatin analogs has been reported to be an effective imaging method for diagnosing NETs [2, 6, 7].

In several previous studies, SSTR-targeting PET imaging was compared with SPECT or SPECT/CT [10, 11], and PET was reported to exhibit higher diagnostic sensitivity than SPECT/CT. However, to our knowledge, quantitative measurements from the two imaging methods have not been directly compared with each other, while quantitative indices are now widely used for imaging evaluation including ^{68}Ga -DOTATOC PET and ^{111}In -pentetreotide SPECT [7].

In this study, we compared the diagnostic sensitivity and quantitative indices between ^{111}In -pentetreotide SPECT/CT and ^{68}Ga -DOTATOC PET/CT.

Materials and Methods

Patients

Patients at our institution who were clinically diagnosed with or suspected to have NET were prospectively enrolled in this study. The diagnosis was made by histopathologic biopsy or biochemical laboratory tests for serum parathyroid hormone, FGF-23, calcium and phosphorus levels, with or without radiological imaging. ^{68}Ga -DOTATOC PET/CT and ^{111}In -pentetreotide scans combined with additional SPECT/CT were performed within 1 month from each other. The study design was approved by the Institutional Review Board of our institution, and written informed consents were obtained from patients.

Image Acquisition

^{111}In -pentetreotide was labeled at our institution using a labeling kit (OcteroScan, Mallinckrodt, Petten, The Netherlands). Briefly, sterile ^{111}In -chloride solution was injected into the OcteroScan reaction vial, which was shaken until its contents were fully dissolved, and the ^{111}In -pentetreotide solution was

incubated at room temperature for more than 30 min. Radiochemical purity was tested with thin-layer chromatography and confirmed to be over 90 %. ^{111}In -pentetreotide (222 MBq) was injected intravenously, and a whole-body scan was performed 4 h after injection using the dual-head gamma camera equipped with medium-energy general-purpose collimators of a hybrid SPECT/CT scanner (Discovery NM/CT 670, GE Healthcare). The photopeak was centered at 173 and 247 keV, with the energy window open by $\pm 20\%$.

At 24 h after injection, a second whole-body scan and additional SPECT/CT images were obtained with the same SPECT/CT scanner. The imaging field of SPECT/CT was determined based on the image findings of the ^{111}In -pentetreotide whole-body scan. All lesions on the ^{111}In -pentetreotide whole-body scan were included in the imaging field of SPECT/CT. When all lesions could not be covered in one bed position of the SPECT/CT, another SPECT/CT was acquired. SPECT was acquired using the same conditions as those of the planar scan, and images were reconstructed on a 64×64 matrix using an iterative algorithm (iteration 8, subset 8). Afterward, a low-dose CT scan for attenuation correction and lesion localization was acquired (130 kVp, 15 mAs), and images were reconstructed into 5-mm-thick slices.

^{68}Ga -DOTATOC was prepared at our institution. Briefly, $^{68}\text{GaCl}_3$ was milked from a generator system (Eckert & Ziegler, Berlin, Germany) and added to the buffer solution (pH 4–5) containing DOTATOC. The solution was heated and purified by passing through a 0.22- μm sterile membrane filter. The solution was diluted with normal saline, and the quality was verified by radiochemical purity, pH, bacterial endotoxin, sterility and residual solvent tests.

Patients were intravenously injected with ^{68}Ga -DOTATOC (1.60 MBq/kg), and PET/CT was performed 1 h after injection using a dedicated PET/CT scanner (Biograph mCT 64, Siemens Medical Solutions). A low-dose CT scan (120 kVp, 50 mAs) was acquired for attenuation correction and anatomical localization. CT images were reconstructed into 5-mm-thick slices. Afterwards, PET images from the vertex to the proximal thigh were obtained for 2 min per bed position (6–7 bed positions per patient), and images were reconstructed by an iterative algorithm (iteration 2, subset 21).

Image Analysis

SPECT/CT and PET/CT fusion images were analyzed using a vendor-provided analysis software package (Syngo.via, Siemens Medical Solutions). All images were reviewed by two experienced nuclear medicine physicians, and decisions were made by consensus. On visual analysis, abnormal uptake was determined as a positive lesion when a lesion exhibited non-physiological increased uptake that was discernible from the background.

For quantitative analysis, the maximal standard uptake value (SUVmax) of each positive lesion was measured on ^{68}Ga -DOTATOC PET/CT images. As reference background tissue, spherical volumes of interest (VOIs) with 1.5-cm diameter were manually drawn in the bilateral lungs, and the mean SUV (SUVmean) of the VOIs was measured. On ^{111}In -pentetateotide SPECT/CT images, the maximal uptake count of a lesion and mean uptake count of the lungs were measured by drawing VOIs using the same method. On both PET/CT and SPECT/CT, the target-to-normal lung ratio (TNR) was measured for each lesion.

Statistical Analysis

Data are expressed as mean $\pm$ SD. Wilcoxon signed rank test, McNemar test and Spearman correlation analysis were used to compare data between groups. Data were analyzed with a commercial statistics software package (SPSS version 21.0, IBM Software, Chicago, IL, USA). *P*-values less than 0.05 were regarded as statistically significant.

Results

Patients

Thirteen patients (7 males and 6 females, mean age 57 ± 17 years) were included in the final analysis, and patient characteristics are summarized in Table 1. Initial diagnosis was made by histopathologic biopsy in nine patients and by biochemical laboratory tests in four. Among them, a total of 35 positive lesions were detected in 10 patients on either the ^{111}In -pentetateotide scan with SPECT/CT or ^{68}Ga -DOTATOC PET/CT: 14 in the liver, 14 in the pancreas, 3 in the spleen, 2

in the brain, 1 in the thoracic spine (T8 vertebral body) and 1 in the thoracic lymph node. Three patients did not exhibit any positive lesions on either imaging method. In two patients with pancreatic and brain lesions, SPECT/CT was acquired twice to include all lesions.

Comparison of Visual Analysis

On the ^{111}In -pentetateotide scan with SPECT/CT, 19 positive lesions were detected: 8 in the liver, 5 in the pancreas, 2 in the spleen, 2 in the brain, 1 in the thoracic spine and 1 in the thoracic lymph node. In the part scanned with SPECT/CT, no lesions were detected on SPECT/CT without presenting on a planar scan. On the ^{68}Ga -DOTATOC PET/CT, 16 additional lesions were detected in comparison with ^{111}In -pentetateotide imaging (6 in the liver, 9 in the pancreas and 1 in the spleen). Notably, 64 % (9/14) of positive lesions in the pancreas were detected only on ^{68}Ga -DOTATOC PET/CT. In contrast, no lesions were detected only on ^{111}In -pentetateotide imaging without presenting on ^{68}Ga -DOTATOC PET/CT. The diagnostic sensitivity of ^{68}Ga -DOTATOC PET/CT was significantly higher than that of ^{111}In -pentetateotide SPECT/CT (100 % vs. 54 %, $P<0.001$).

Comparison of Quantitative Analysis

On ^{68}Ga -DOTATOC PET/CT, the SUVmax of positive lesions and SUVmean of the lungs were 32.0 ± 23.4 and 0.4 ± 0.2 , respectively, and the TNR was calculated to be 99.3 ± 84.3 . The lesions in the liver and pancreas exhibited relatively high TNR values (Table 2). On ^{111}In -pentetateotide SPECT/CT, the TNR was calculated to be 71.1 ± 114.9 (mean uptake count of the lungs = 26.2 ± 14.1). Like the PET/CT findings, the TNR was relatively high in the liver and pancreas lesions.

Table 1 Patient characteristics

No.	Age (years)	Sex	Diagnostic method	Location of lesions
1	34	F	Pathology	Pancreas, thoracic lymph node
2	72	M	Pathology	Liver
3	45	M	Pathology	Pancreas
4	68	F	Biochemical laboratory tests	No detected lesion
5	20	M	Pathology	Pancreas, thoracic spine (T8)
6	42	F	Pathology	Pancreas
7	64	M	Pathology	Pancreas, brain
8	21	F	Biochemical laboratory tests	No detected lesion
9	67	F	Pathology	Pancreas
10	57	F	Biochemical laboratory tests	Pancreas, brain
11	63	M	Pathology	Liver, spleen
12	57	M	Biochemical laboratory tests	No detected lesion
13	54	M	Pathology	Pancreas

Table 2 TNR values in ^{68}Ga -DOTATOC PET/CT and ^{111}In -pentetreotide SPECT/CT

Organ	Lesions detected on both (<i>n</i> =19)		Lesions detected on PET/CT only (<i>n</i> =16)		Overall (<i>n</i> =35)	
	^{68}Ga PET/CT	^{111}In SPECT/CT	^{68}Ga PET/CT	^{111}In SPECT/CT	^{68}Ga PET/CT	^{111}In SPECT/CT
Pancreas	128.3±111.1	69.3±77.5	88.5±74.3	40.0±41.5	102.7±87.1	50.5±55.9
Liver	155.6±98.6	175.7±203.0	99.0±50.2	39.4±14.2	131.3±83.9	117.3±164.8
Spleen	24.5±4.5	33.5±1.9	36.8	31.4	28.6±7.8	32.8±1.8
Brain	10.7±2.1	3.7±0.4	—	—	10.7±2.1	3.7±0.4
Thoracic spine	62.8	16.8	—	—	62.8	16.8
Thoracic LN	30.2	16.2	—	—	30.2	16.2
Overall	107.9±99.6	97.9±149.9	89.2±63.3	39.3±31.5	99.9±84.3	71.1±114.9

TNR values measured on ^{68}Ga -DOTATOC PET/CT and ^{111}In -pentetreotide SPECT/CT exhibited a significant correlation with each other ($r=0.692$, $P=0.01$; Fig. 1). However, the TNR values on ^{68}Ga -DOTATOC PET/CT were significantly higher than those on ^{111}In -pentetreotide SPECT/CT ($P<0.001$).

Images of representative cases are shown in Figs. 2 and 3.

Discussion

In this study, we directly compared the diagnostic sensitivity as well as quantitative indices between ^{111}In -pentetreotide SPECT/CT and ^{68}Ga -DOTATOC PET/CT. ^{68}Ga -DOTATOC PET/CT was demonstrated to have a higher diagnostic sensitivity than ^{111}In -pentetreotide SPECT/CT. In addition, the TNR on PET/CT was significantly higher than on SPECT/CT, although there was a considerable correlation between them.

Fig. 1 TNR values measured on ^{68}Ga -DOTATOC PET/CT and ^{111}In -pentetreotide SPECT/CT. A significant positive correlation existed between the two measurements

SSTR has been extensively attempted as a target for diagnosis and treatment in NET [12]. ^{111}In -pentetreotide has been used for SSTR imaging for more than 2 decades, and in recent years, ^{68}Ga -labeled somatostatin analogs have been used for PET imaging [2, 6]. Although SPECT is possible with ^{111}In -pentetreotide, PET using ^{68}Ga -labeled agents has the advantage of high image quality. Additionally, PET can provide information on the exact anatomical location because most current PET scanners are hybrid PET/CT scanners, and it is more cost-effective than ^{111}In -pentetreotide scans because it avoids unnecessary CT or MRI [13]. Therefore, several studies have reported that the diagnostic performance of SSTR PET is higher than that of ^{111}In -pentetreotide SPECT [7, 10, 11]. However, SPECT/CT has recently become available in many institutions, and attenuation correction and anatomical localization are also available for ^{111}In -pentetreotide imaging. Thus, we compared both imaging techniques in terms of diagnostic sensitivity and quantitative indices in the current study.

In a previous study where diagnostic performance was directly compared in the same patients between ^{68}Ga -DOTATATE PET/CT and $^{99\text{m}}\text{Tc}$ -HYNIC-octreotide SPECT/CT, PET/CT exhibited a significantly higher sensitivity (96 %) than SPECT/CT (60 %) [10]. Also in our study, the sensitivity of ^{68}Ga -DOTATOC PET/CT was 100 %, whereas that of ^{111}In -pentetreotide SPECT/CT was 54 %. This difference may be elucidated chiefly by differences in imaging characteristics. Compared with SPECT, PET has higher spatial resolution, higher sensitivity for signals and consequently higher image quality. Thus, in spite of the attenuation correction and lesion localization with combined CT, SPECT/CT exhibited lower TNR values and a lower sensitivity than PET/CT in our study. However, the difference may be partially elucidated by the different characteristics of imaging agents. Currently, there are several somatostatin analogs for SSTR PET imaging, such as ^{68}Ga -DOTANOC, ^{68}Ga -DOTATOC and ^{68}Ga -DOTATATE. Although no significant difference was reported among the diagnostic performances of these agents [10, 11, 14], each one

Fig. 2 A 34-year-old female patient with a pancreatic neuroendocrine tumor. Two focal lesions were detected in the pancreatic head on ^{68}Ga -DOTATOC PET/CT (a–c). The TNR of each lesion was calculated as 115.5 and 117.8, respectively. On ^{111}In -pentetreotide SPECT/CT (d), only mild uptake was observed at the lesions, and the TNR was 40.0 and 22.5, respectively

exhibited some specific characteristics. For example, DOTATOC has a high binding affinity to SSTR 2 and 5 [10, 11, 15].

In addition to the high sensitivity, ^{68}Ga -DOTATOC PET/CT also has the advantage of patient convenience. ^{68}Ga -DOTATOC PET can be acquired only 1 h after injection, and overall the imaging time is less than 2 h, whereas an ^{111}In -pentetreotide scan is usually acquired 24 h after the injection. Because of its high sensitivity and convenience, SSTR PET can be used for every aspect of NET management. Ambrosini et al. reported that ^{68}Ga -DOTANOC PET/CT is an effective method for staging, restaging and treatment

monitoring of NETs [16]. Also, Naswa et al. reported that ^{68}Ga -DOTANOC PET/CT is useful for detecting NET lesions when lesions are negative or equivocal on radiological imaging such as CT and MRI [6]. Similarly, ^{68}Ga -DOTANOC PET/CT is an effective imaging method for finding primary sites in case of hepatic metastasis of NET from unknown primary sites [17]. Thus, it was reported that ^{68}Ga -DOTATATE PET/CT changed the treatment of choice in 60 % of NET patients [18]. Moreover, SSTR PET is used for planning peptide receptor radiation therapy (PRRT), which is a promising treatment modality in case of inoperable or metastatic NETs [19]. It has been reported that SUVmax on

Fig. 3 A 72-year-old male patient who had undergone laparoscopic distal pancreatectomy because of a neuroendocrine tumor. During follow-up, multiple hepatic metastatic lesions were detected on ^{68}Ga -DOTATOC PET/CT (a–c). Although multiple lesions were also detected on ^{111}In -pentetreotide SPECT/CT (d), more lesions were detected on ^{68}Ga -DOTATOC PET/CT compared with ^{111}In -pentetreotide SPECT/CT. The TNR of the largest lesion was calculated to be 275.9 in ^{68}Ga -DOTATOC PET/CT and 634.4 on ^{111}In -pentetreotide SPECT/CT, respectively

^{68}Ga -DOTATOC PET/CT is well correlated with the response to PRRT in NETs [20].

Quantitative indices have recently been increasingly used for analyzing clinical molecular imaging. In case of ^{18}F -fluorodeoxyglucose PET, the SUVmax and metabolic volume indices are commonly used for lesion characterization and tumor burden quantification [21]. Additionally, the tumor-to-normal organ ratio is also often used as an index for evaluating the metabolism of a lesion by setting the liver as a normal reference organ [22]. In SSTR PET, using the spleen as a normal reference organ was attempted in a previous study [23]. In the current study, we calculated the TNR by setting the lungs as a normal reference organ. The lung has also been reported as a normal reference organ in previous studies [24–26]. In the lungs, the physiological or non-specific uptake of ^{68}Ga -DOTATOC and ^{111}In -octreotide is low [7, 27]. Additionally, the lungs were included in the imaging field of every SPECT/CT imaging in our study, and they were used for TNR calculation.

In spite of a considerable correlation between the TNR values of the two imaging methods, the overall sensitivity and TNR values of ^{111}In -pentetreotide SPECT/CT were lower than those of ^{68}Ga -DOTANOC PET/CT. Thus, it can be suggested that ^{111}In -pentetreotide may be inappropriate for meticulous evaluation of NET, particularly regarding PRRT planning. Although scan-based or SPECT/CT-based dosimetry and radioisotope treatment planning have been available in recent years [28], further studies are required to determine whether ^{111}In -pentetreotide imaging can be used for PRRT planning.

There are some limitations to our study. First, the case number in our study is relatively small, because this is a preliminary report and the study is ongoing. However, the results were statistically significant and in line with those of previous reports. Second, all the lesions analyzed in our study were not pathologically confirmed as NETs. Despite a meticulous review of SSTR imaging and radiological imaging, false-positive lesions may have been included in the analysis. However, the specificity and positive predictive value of SSTR imaging have been reported to be over 95 % [10], so false-positive lesions would not be a critical bias factor. Third, the SPECT/CT scan does not cover the whole body. Therefore, in the part that is not covered with SPECT/CT, some lesions can be detected on the SPECT/CT although lesions are not detected in the whole-body planar scan.

Conclusions

In conclusion, ^{68}Ga -DOTATOC PET/CT has a higher sensitivity than ^{111}In -pentetreotide SPECT/CT in the lesion detection of NETs. Although there is a significant correlation between the quantitative indices of the two imaging techniques,

the values are significantly different from each other. Thus, if ^{111}In -pentetreotide SPECT/CT is used for meticulous NET evaluation instead of ^{68}Ga -DOTATOC PET/CT, it should be used carefully.

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Conflict of Interest Inki Lee, Jin Chul Paeng, Soo Jin Lee, Chan Soo Shin, Jin-Young Jang, Gi Jeong Cheon, Dong Soo Lee, June-Key Chung and Keon Wook Kang declare that they have no conflict of interest.

Ethics Statement This prospective study was approved by the Institutional Review Board at Seoul National University Hospital (IRB no. 1404-095-573), and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards

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