Journal of Nuclear Medicine, published on November 1, 2019 as doi:10.2967/jnumed.119.235093

Head-to-head comparison of ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT in patients with metastatic, well-differentiated neuroendocrine tumors: a prospective study

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Word count: 4814

Short running title: ^{68}Ga-DOTA-JR11 PET/CT in NET

Disclosure

This work was sponsored in part by the National Natural Science Foundation of China (81571713, 81601529), CAMS Innovation Fund for Medical Sciences (2016-I2M-4-003), CAMS initiative for innovative medicine (2017-I2M-4-002, 2018-I2M-3-001), Tianjin Natural Science Foundation (18JCQNJC11600), and Tianjin Medical University Basic Research Foundation (2018KJ060). No other potential conflicts of interest relevant to this article exist.

ABSTRACT

Purpose:

^{68}Ga-DOTA-JR11 is a somatostatin receptor subtype 2 (SSTR2) specific antagonist used for PET/CT imaging. The purpose of this study is to compare ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT in patients with metastatic, well-differentiated neuroendocrine tumors.

Methods:

Patients with histologically-proven, metastatic and/or unresectable, well-differentiated neuroendocrine tumors were prospectively recruited in this study. Each of them received an intravenous injection of ^{68}Ga-DOTATATE (155 MBq ± 52 MBq)) on the first day and ^{68}Ga-DOTA-JR11 (148 ± 52 MBq) on the second day. Whole-body PET/CT scans were performed at 40 to 60 minutes after injection on the same scanner. Physiologic uptake of normal organs, lesion numbers, and lesion uptake were compared.

Results:

Thirty-one patients were prospectively enrolled in the study. The SUVmax of the spleen, renal cortex, adrenal glands, pituitary glands, stomach wall, normal liver parenchyma, small intestine, pancreas, and bone marrow were significantly lower on ^{68}Ga-DOTA-JR11 than on ^{68}Ga-DOTATATE PET/CT ($P < 0.001$). ^{68}Ga-DOTA-JR11 detected significantly more liver lesions (552 vs. 365, P=0.001), but fewer bone lesions (158 vs. 388, P=0.016) than ^{68}Ga-DOTATATE. The target-to-background of liver lesions was significantly higher on ^{68}Ga-DOTA-JR11 (7.7±5.4 vs. 3.4±2.0, $P < 0.001$). ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT showed comparable results for primary tumors and lymph node metastases based on either patient-based or lesion-based comparison.

Conclusion:

^{68}Ga-DOTA-JR11 performs better in the detection ability and tumor-to-background ratio of liver metastases, while ^{68}Ga-DOTATATE may outperform ^{68}Ga-DOTA-JR11 in the detection of bone metastases. However, the lower SSTR2 affinity of ^{68}Ga-DOTA-JR11 compared to ^{177}Lu-DOTA-JR11 may limit its role as a diagnostic pair for the theranostic approach with ^{177}Lu-DOTA-JR11.

Key Words:

Somatostatin receptor antagonist, ^{68}Ga-DOTA-JR11, ^{68}Ga-DOTATATE, neuroendocrine tumor, PET/CT

INTRODUCTION

Somatostatin receptor (SSTR), especially SSTR subtype 2, is the key target for the theranostic approach of neuroendocrine tumors (NETs). With different isotopes labelled, radiolabeled somatostatin analogues have been used clinically either for imaging or peptide receptor radionuclide therapy (PRRT) (*1-3*). Since the approval of Octreoscan by FDA in 1994, many ^{68}Ga labelled molecules for imaging purpose have emerged, such as DOTATATE, DOTATOC, and DOTANOC. SSTR PET/CT imaging plays an important role in the primary tumor detection, staging, and restaging of NETs. Furthermore, as the imaging half of theranostics, it provides key information in deciding whether the patients are eligible for PRRT. All these mentioned agents, which are SSTR agonists could be internalized into tumor cells after the ligand/receptor interaction (*4*).

An important development in the field of SSTR targeting was the recent introduction of SSTR antagonists (*5-10*). Results of the first radiolabeled antagonists were published in 1996 by Bass et al (*11*). Radiolabeled LM3, JR10, and JR11, the second generation of antagonists (*12*), have been developed and evaluated in patients with NETs (*7*). Despite lack of internalization, preclinical and clinical studies suggested that radiolabeled SSTR antagonists may perform better than agonists (*5,6*). They showed more favorable pharmacokinetics, better image contrast, higher tumor uptake and residence time. The possible reason is that antagonists can recognize more binding sites on receptors. Recently, the first-in-human study of ^{68}Ga-DOTA-JR11 conducted by Krebs et al showed good safety and biodistribution profiles in patients with metastatic NETs (*13*). Rapid tumor uptake, high tumor/background ratios, and rapid clearance from blood were demonstrated in the study. Nicolas et al directly compared the sensitivity of ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATOC and found that

antagonists were superior in terms of sensitivity, lesion detection, and image contrast compared with agonists (*14,15*).

With antagonists, we now have an alternative choice to agonists. However, there is still not much evidence about the performance of PET/CT imaging with SSTR antagonists. Hence, we designed this prospective study to compare ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 PET/CT in patients with metastatic, well-differentiated NETs.

MATERIALS AND METHODS

Study Design and Patient Population

This study was approved by the institutional review board of Peking Union Medical College Hospital and all subjects signed a written informed consent before study participation. Patients with histologically-proven, metastatic and/or unresectable, well-differentiated neuroendocrine tumors (G1 or G2) were prospectively and consecutively recruited in this study. To avoid the influence of radiolabeled somatostatin analogue treatment on imaging, patients received long-acting radiolabeled somatostatin analogue treatment within 4 weeks before the study were excluded (*16*). The two PET/CT scans were conducted on two consecutive days.

^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 Preparation

GMP-grade precursor, DOTA-JR11 and DOTATATE were supplied by CS Bio Co. (20 Kelly Court Menlo Park, CA94025 USA) and ABX GmbH (Germany), respectively. Radiolabeling procedure was performed manually in a hot cell. Briefly, $^{68}GaCl_3$ eluent was eluted from a ^{68}Ge/^{68}Ga

generator (Eckert & Ziegler, Germany) using 5ml of 0.1 mol/L hydrochloride acid (HCl). The elute was added into a reaction vial containing the precursor (for DOTA-JR11, 80μg; for DOTATATE, 40μg) and dissolved in sodium acetate buffer, for a final reaction mixture pH of 4. The mixture was heated to 100 °C for 10 min. After cooling to room temperature, the reaction mixture was diluted with 5 mL water and then loaded onto a C18 light SEP-PAK cartridge (preconditioned with 10 mL ethanol and 10 mL water in advance) and washed with normal saline to remove unincorporated radionuclide. Finally, the product was eluted off the cartridge with 75% ethanol solution and diluted with saline and passed through a Millipore filer (0.22 μm, 25 mm) into a sterile product vial. The radiochemical purity of the final product was >95%.

^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 PET/CT Imaging

The study was carried out on a time-of-flight PET/CT scanner (Polestar m660, SinoUnion Healthcare Inc., China) on two consecutive days. Patients received an intravenous injection of ^{68}Ga-DOTATATE (155 MBq ± 52 MBq) on the first day and ^{68}Ga-DOTA-JR11 (148 ± 52 MBq) on the second day. A low-dose CT scan (120KeV; 100 mAs; 1.3 pitch; 2.5 mm slice thickness; 0.5 s rotation time; estimated radiation dose 9.0 mGy) from head to proximate thigh was obtained at 40-60 min post-injection for anatomical localization and attenuation correction. PET scanning followed at 2min/bed position with a 23-slice overlap. Images were reconstructed using an ordered subsets expectation maximization algorithm (2 iterations, 10 subsets, 192×192 matrix) and corrected for CT-based attenuation, dead time, random events, and scatter.

Adverse Events Monitoring

Vital signs (blood pressure, body temperature, and heart rate) and clinical symptoms were monitored and recorded within 2 hours post-injection according to version 4.03 of the Common Terminology Criteria for Adverse Events.

Image Interpretation and Data Analysis

The images were reviewed on MIM software (MIM Software Inc., Cleveland, OH). One experienced nuclear medicine expert (25 years of experience in nuclear medicine), masked to the patient and medical history, reviewed the images.

For normal tissues, the physiologic uptake of ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 were compared in the following organs: spleen, renal cortex, adrenal glands, pituitary gland, stomach, normal liver parenchyma, small intestine, and pancreas (uncinate process). Regions of interest were drawn over the organs excluding focal lesions. Meanwhile, any activity from adjacent organs such as renal pelvis and urinary bladder was avoided. SUVmax (using body weight normalization) of the regions of interest in normal organs were recorded. In case of bilateral organs such as adrenal glands and renal cortex, the average SUVmax were calculated.

Any focal accumulations of ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 not explained by physiologic uptake were interpreted as focal lesions. Volumes of interest of focal lesions were segmented using PET Edge, a gradient-based segmentation algorithm (*17*). The number and SUVmax of focal lesions were recorded. For liver and splenic lesions, relative uptake of focal lesions was quantified using target-to-background ratio (TBR), defined as SUVmax (lesion)/SUVmax (normal parenchyma).

Comparative analysis of SUVmax and TBR between ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 was conducted for matched lesions only.

Statistical Analysis

Data was were expressed as mean ± SD values. The differences of SUVmax and TBR between ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE were evaluated using paired t-test (SPSS, version 22). Statistical comparison of the lesion numbers was conducted using sign tests. P value < 0.05 was considered to indicate statistically significant.

RESULTS

Thirty-one patients were prospectively enrolled in the study. The clinical characteristics are summarized in Supplemental Table 1. No patient received treatment between ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 PET/CT. Both tracers were tolerated well in all patients. No adverse events were reported.

Biodistribution Comparison Between ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 PET/CT

Unlike ^{68}Ga-DOTATATE, ^{68}Ga-DOTA-JR11 demonstrated minimal or mild uptake in almost all organs except for urinary tract (Fig. 1). The SUVmax of spleen, renal cortex, adrenal glands, pituitary glands, stomach wall, normal liver parenchyma, small intestine, pancreas, and bone marrow are shown in Table 1. The uptake of all listed normal organs was significantly lower on ^{68}Ga-DOTA-JR11 than on ^{68}Ga-DOTATATE PET/CT (P < 0.001).

Comparison of Tumor Detection Rates Between ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 PET/CT

A total of 835 and 875 focal lesions were depicted on ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT, respectively (P=0.152; Table 2).

On patient-based comparison, ^{68}Ga-DOTA-JR11 demonstrated a higher detection ability for liver lesions (Fig. 1). In 26 patients with liver metastases, 54% (14/26) of patients showed more liver metastases on ^{68}Ga-DOTA-JR11 compared with ^{68}Ga-DOTATATE, while 42% (11/26) of patients demonstrated comparable results. Only 1 patient had fewer liver lesions detected on ^{68}Ga-DOTA-JR11 PET/CT. For bone lesions, however, ^{68}Ga-DOTA-JR11 is inferior to ^{68}Ga-DOTATATE in 78% (7/9) of patients (Fig. 2).

On lesion-based comparison, ^{68}Ga-DOTA-JR11 detected significantly more liver lesions (552 vs. 365, P=0.001), but fewer bone lesions (158 vs. 388, P=0.016; Fig. 3). ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT showed comparable results for primary tumors and lymph node metastases based on either patient-based or lesion-based comparison.

Uptake Comparison Between ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 PET/CT

For matched lesions, ^{68}Ga-DOTA-JR11 demonstrated significantly lower uptake in all lesions (Table 3). The TBR of liver lesions, however, were significantly higher on ^{68}Ga-DOTA-JR11 than ^{68}Ga-DOTATATE (7.7±5.4 vs. 3.4±2.0, P < 0.001). The two matched splenic lesions also showed higher TBR on ^{68}Ga-DOTA-JR11 PET/CT.

DISCUSSION

Our study prospectively compares the lesion detection rates between SSTR antagonist, ^{68}Ga- DOTA-JR11 and agonist, ^{68}Ga-DOTATATE, in a single group of patients. The results show that ^{68}Ga-DOTA-JR11 has higher lesion detection rate than ^{68}Ga-DOTATATE in the detection of liver metastases. For bone lesions, however, ^{68}Ga-DOTA-JR11 is inferior to ^{68}Ga-DOTATATE.

^{68}Ga-DOTA-JR11 showed an overall lower tumor uptake compared with ^{68}Ga-DOTATATE, which may have two reasons. The first reason lies in the different SSTR2 affinities of ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE. ^{68}Ga-DOTATATE has a much higher SSTR2 affinity than ^{68}Ga-DOTA-JR11 (50% inhibitory concentration (IC_{50}) is 0.2 nmol/L vs. 29 nmol/L) (*7*). This is likely to have a negative impact on tumor uptake of ^{68}Ga-DOTA-JR11 which is in fact worse than that of ^{68}Ga-DOTATATE. An additional reason for the lower tumor uptake of ^{68}Ga-DOTA-JR11 might be SSTR2 saturation/internalization after injection of 40μg ^{68}Ga-DOTATATE 24 hours ahead of ^{68}Ga-DOTA-JR11 PET/CT. JC Reubi et al. showed in human NET tissue less receptor binding of the SSTR2 specific antibody on the cell membrane after injection of 200 μg Octreotide (*4*). This might be relevant even after injection of only 40μg ^{68}Ga-DOTATATE as ^{68}Ga-DOTATATE has a 10 times higher affinity for SSTR2 than Octreotide (*12*). These two reasons explain not only the lower tumor uptake of ^{68}Ga-DOTA-JR11 but also, at least in part, the inferiority of ^{68}Ga-DOTA-JR11 in the detection of bone metastases, which will be further discussed below.

Nicolas et al. prospectively compared ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATOC in the same patients and they found comparable tumor uptake between the two tracers ($P > 0.05$ in all lesions). The

seemingly contradicting results may again be explained by the different SSTR affinities. ^{68}Ga-NODAGA-JR11 has a comparable SSTR2 affinity to ^{68}Ga-DOTATOC (IC_{50} is 1.2 nmol/L vs. 2.5 nmol/L), which is much higher than that of ^{68}Ga-DOTA-JR11 (IC_{50} is 29 nmol/L). It indicates that ^{68}Ga-DOTA-JR11 might not be the ideal diagnostic pair for a theranostic approach with ^{177}Lu-DOTA-JR11 as ^{177}Lu-DOTA-JR11 has a much better SSTR2 affinity than ^{68}Ga-DOTA-JR11 (IC_{50} is 0.73 nmol/L vs. 29 nmol/L). Furthermore, D Reidy-Lagunes et al. found a very good objective response and PFS after 1-2 treatment cycles with ^{177}Lu-DOTA-JR11 in 20 patients with NETs including 7 patients with bone metastases (*18*). It is likely that ^{68}Ga-NODAGA-JR11 is the better diagnostic pair as it has a very similar SSTR2 affinity as ^{177}Lu-DOTA-JR11 (IC_{50} is 1.2 nmol/L vs. 0.73 nmol/L). However, there has been no intra-patient comparative data between ^{68}Ga-DOTA-JR11 and ^{68}Ga-NODAGA-JR11 and further studies are warranted.

Compared with ^{68}Ga-DOTATATE, ^{68}Ga-DOTA-JR11 shows a superior lesion detection ability for liver metastases based on both patient-based and lesion-based comparison. In a prospective study, Nicolas et al compared the sensitivity of ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTA-TOC in metastatic NETs (*14*). They reported an overall higher sensitivity for ^{68}Ga-NODAGA-JR11, which was mainly due to more liver lesion detected. Our study further supports the superiority of ^{68}Ga-DOTA-JR11 over ^{68}Ga-DOTATATE on liver lesion detection. It's probably caused by lower liver background uptake and more binding sites on SSTR receptors recognized by antagonist. Nevertheless, our study shows that the bone lesion detect ability of ^{68}Ga-DOTA-JR11 is remarkably inferior to that of ^{68}Ga-DOTATATE. Imaging comparison of bone metastases using antagonist and agonist has not been previously reported. The low affinity of ^{68}Ga-DOTA-JR11 to bone metastases might be overlooked in previous studies. The

preliminary results of PRRT using antagonists reported by Wild et al found a 1.1 to 7.2 times higher tumor to kidney/bone marrow uptake ratio of ^{177}Lu-DOTA-JR11 compared with ^{177}Lu-DOTATATE (*19*). Nevertheless, only four patients were included in that study and no bone lesions were present. Bone metastases were also not specified in the study by Nicolas group (*14*).

The results of ^{68}Ga-DOTA-JR11 tumor uptake are comparable to that of previous study (*13*) for bone (7.8 ± 5.4 versus 6 ± 3) and lymph node metastases (14.4 ± 10.3 versus 14 ± 20), but lower for liver lesions(18.6 ± 12.5 versus 25 ± 22). A possible reason is that we included lesions regardless of the size criteria as long as they're identifiable on PET images. It significantly increases the number of liver lesions detected (552 in 26 patients versus 30 in 20 patients), which decreases the average SUVmax since small lesions tend to have relatively lower uptake due to partial volume effect (*20*). Besides, saturation/internalization of SSTR2 receptors after ^{68}Ga-DOTATATE injection may be another possible reason for low liver lesion accumulation. The image contrast for liver lesions, however, is significantly higher on ^{68}Ga-DOTA-JR11 PET/CT. This is, again, mainly due to the much lower uptake of normal liver parenchyma on ^{68}Ga-DOTA-JR11 PET/CT (2.8±0.9 vs. 9.7±3.0, $P < 0.001$). It is the same for splenic lesions although no statistical comparison was conducted due to limited lesion numbers.

As a potential diagnostic companion of ^{177}Lu-DOTA-JR11, the biodistribution of ^{68}Ga-DOTA-JR11 in normal organs and tumor uptake are very important in deciding whether the patients are eligible for PRRT with ^{177}Lu-DOTA-JR11. Our study demonstrated a more favorable biodistribution of ^{68}Ga-DOTA-JR11 than ^{68}Ga-DOTATATE in patients with metastatic NETs, with minimal or mild uptake in almost all organs except for urinary tract. The low background activity provides an excellent image contrast, especially in liver, which is the predominant site of metastases in patients with

gastroenteropancreatic NETs (*21*). A lower uptake is also observed in renal cortex and bone marrow. However, it does not implicate that renal and bone marrow toxicity is lower with ^{177}Lu-DOTA-JR11 than with ^{177}Lu-DOTATATE. As mentioned before SSTR2 affinity profile varies between ^{68}Ga-DOTA-JR11 and ^{177}Lu-DOTA-JR11. Furthermore, measurement of radiotracer uptake 40-60 minutes after injection supplies limited information to make any dose estimation. In fact, D Wild et al showed in a prospective cross-over comparison of ^{177}Lu-DOTA-JR11 and ^{177}Lu-DOTATATE in the same patient no higher kidney or bone marrow dose with ^{177}Lu-DOTATATE compared to ^{177}Lu-DOTA-JR11 (*19*). At the same time tumor dose was higher with ^{177}Lu-DOTA-JR11 than with ^{177}Lu-DOTATATE. For organs with known SSTR expression, such as pituitary glands, adrenal glands, and spleen, there is either no or minimal uptake on ^{68}Ga-DOTA-JR11 PET/CT. Besides, lack of uptake is also observed in stomach wall, small intestine, and uncinate process of pancreas, which usually demonstrate moderate uptake on ^{68}Ga-DOTATATE PET/CT. This phenomenon is described in the previous study by Krebs et al (*13*) and currently not well understood. Irrespective of the cause, the low uptake in these organs is considered a major advantage of antagonist over agonist for potential detection of more lesions. It also helps to differentiate between physiologic uptake and real lesions.

In previous study comparing ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTA-TOC, the median (interquartile range) time between the two scans was 34 [27.5-135] days (*14*). Although NETs are relatively slow growing tumors, disease progression during such a long time can still have a potential influence on imaging studies. Therefore, in our study, the ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT were done on two consecutive days to minimize the impact of disease progression. However, it may also be a limitation of this study. As we have discussed, the 40μg load of ^{68}Ga-DOTATATE 24 hours ahead

might be a cause of lower tumor uptake of 68Ga-DOTA-JR11 due to SSTR2 saturation/internalization. Besides, our study is limited by lack of reference imaging studies, such as contrast enhanced computed tomography or magnetic resonance imaging. Hence, the sensitivity of ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT can't be calculated and further comparative studies are required.

CONCLUSION

^{68}Ga-DOTA-JR11 performs better in the detection ability and tumor-to-background ratio of liver metastases, while ^{68}Ga-DOTATATE may outperform ^{68}Ga-DOTA-JR11 in the detection of bone metastases. However, the lower SSTR2 affinity of ^{68}Ga-DOTA-JR11 compared to ^{177}Lu-DOTA-JR11 may limit its role as a diagnostic pair for the theranostic approach with ^{177}Lu-DOTA-JR11.

DISCLOSURE

This work was sponsored in part by the National Natural Science Foundation of China (81571713, 81601529), CAMS Innovation Fund for Medical Sciences (2016-I2M-4-003), CAMS initiative for innovative medicine (2017-I2M-4-002, 2018-I2M-3-001), Tianjin Natural Science Foundation (18JCQNJC11600), and Tianjin Medical University Basic Research Foundation (2018KJ060). No other potential conflicts of interest relevant to this article exist.

ACKNOWLEDGMENTS

We'd like to thank all the patients who participated in this study. We also would like to thank Yue Zhang (SinoUnion Healthcare Inc., China) for image acquisition and data collection and Dr. Chengyan

Dong (GE Healthcare, China) for critical proof-reading and figure suggestions.

KEY POINTS

QUESTION: Does PET/CT with somatostatin receptor (SSTR) antagonist, ^{68}Ga-DOTA-JR11, has better lesion detection ability than agonist, ^{68}Ga-DOTATATE, in patients with metastatic, well-differentiated neuroendocrine tumors?

PERTINENT FINDINGS: Thirty-one patients with metastatic, well-differentiated neuroendocrine tumors were prospectively recruited to compare the lesion detection ability of ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT. ^{68}Ga-DOTA-JR11 performs better in detecting liver metastases, while ^{68}Ga-DOTATATE outperforms ^{68}Ga-DOTA-JR11 in the detection of bone metastases.

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga-DOTA-JR11 is an optional alternative to SSTR agonists in patients with NETs, especially in liver-dominant metastases.

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Table 1. Comparison of normal organ uptake between ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTATATE PET/CT

SUVmax	JR11	TATE	P value
Spleen (n=29) *	3.2 ± 1.3	22.5 ± 8.0	< 0.001
Renal cortex (n=31)	6.7 ± 1.6	14.6 ± 3.8	< 0.001
Adrenal glands (n=31)	2.1 ± 0.8	11.3 ± 4.4	< 0.001
Pituitary gland (n=31)	2.1 ± 1.6	7.7 ± 3.2	< 0.001
Stomach wall (n=31)	1.9 ± 0.6	7.1 ± 4.2	< 0.001
Normal liver parenchyma (n=31)	2.8 ± 0.9	9.7 ± 3.0	< 0.001
Small intestine (n=31)	1.9 ± 0.5	6.1 ± 1.8	< 0.001
Pancreas (uncinate process, n=25) †	1.7 ± 0.6	4.3 ± 1.9	< 0.001
Bone marrow (L5 vertebra, n=31)	1.2 ± 0.4	1.6 ± 0.6	< 0.001

Data were expressed as mean ± SD.

* Splenectomy was done in two patients.

† Six patients were rules out for pancreas uptake measurement due to presence of focal lesions in uncinate process or partial/total pancreatectomy.

Table 2. Number of lesions found on ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTA-TATE PET/CT

Patient	Primary tumor		Liver metastases		Bone metastases		Lymph node metastases		Rare metastases		Total lesions	
	JR11	TATE	JR11	TATE	JR11	TATE	JR11	TATE	JR11	TATE	JR11	TATE
1	1	1	13	4	3	15	2	3	-	-	19	23
2	1	1	11	11	-	-	3	3	-	-	15	15
3	1	1	34	34	-	-	2	1	-	-	37	36
4	-	-	-	-	0	6	1	1	-	-	1	7
5	1	1	14	12	-	-	-	-	-	-	15	13
6	1	1	-	-	-	-	3	1	-	-	4	2
7	-	-	7	2	-	-	-	-	-	-	7	2
8	-	-	13	3	-	-	2	1	-	-	15	4
9	2	5	-	-	0	10 *	2	5	-	-	4	20
10	2	2	46	46	12	12	1	1	-	-	61	61
11	1	1	1	0	-	-	-	-	-	-	2	1
12	1	1	64	43	-	-	-	-	-	-	65	44
13	1	1	29	13	-	-	2	1	-	-	32	15
14	1	1	16	2	-	-			-	-	17	3
15	1	1	6	6	-	-	3	1	-	-	10	8
16	-	-	54	27	-	-	-	-	-	-	54	27
17	1	1	48	48	-	-	-	-	-	-	49	49
18	-	-	16	16	-	-	-	-	-	-	16	16
19	-	-	-	-	3	8	6	9	-	-	9	17
20	1	1	36	36	-	-	-	-	-	-	37	37
21	-	-	-	-	39	46	5	5	51 †	51 †	95	102
22	-	-	1	1	-	-	-	-	-	-	1	1
23	1	1	17	17	14	192	3	3	2 ‡	2 ‡	37	215
24	-	-	0	1	-	-	3	3	-	-	3	4
25	-	-	6	0	-	-	-	-	-	-	6	0
26	1	1	69	22	85	85	-	-	9 §	2 §	164	110
27	1	1	21	1	-	-	-	-	-	-	22	2
28	1	1	5	5	-	-	3	3	-	-	9	9
29	-	-	12	6	-	-	1	1	-	-	13	7
30	0	1	2	2	2	14	1	1			5	18
31			11	7							11	7
Sum	20	24	552	365	158	388	43	43	62	55	835	875
P value	0.500		0.001		0.016		0.727				0.152	

* Patient 9 had heterogeneous diffuse osseous uptake of ^{68}Ga-DOTA-TATE. We arbitrarily set the number of osseous lesions to be ten.

† Pleural metastases

‡ Peritoneal metastases

§ Splenic metastases

Table 3. Uptake of matched lesions on ^{68}Ga-DOTA-JR11 and ^{68}Ga-DOTA-TATE PET/CT

	JR11	TATE	P value
	SUVmax		
Primary tumor (n=22)	18.7 ± 17.4	32.1 ± 23.7	0.013
Liver metastases (n=410)	18.6 ± 12.5	27.3 ± 15.4	< 0.001
Bone metastases (n=158)	7.8 ± 5.4	12.5 ± 12.0	< 0.001
Lymph node metastases (n=37)	14.4 ± 10.3	26.3 ± 17.1	< 0.001
Pleural/peritoneal metastases (n=53)	20.2 ± 4.5	26.4 ± 6.8	< 0.001
Splenic metastases (n=2) *	30.6	23.8	
	Tumor-to-background ratio		
Liver metastases (n=410)	7.7 ± 5.4	3.4 ± 2.0	< 0.001
Splenic metastases (n=2) *	6.4	1.4	

Data were expressed as mean ± SD.

* Statistical comparison was not conducted due to limited matched lesions

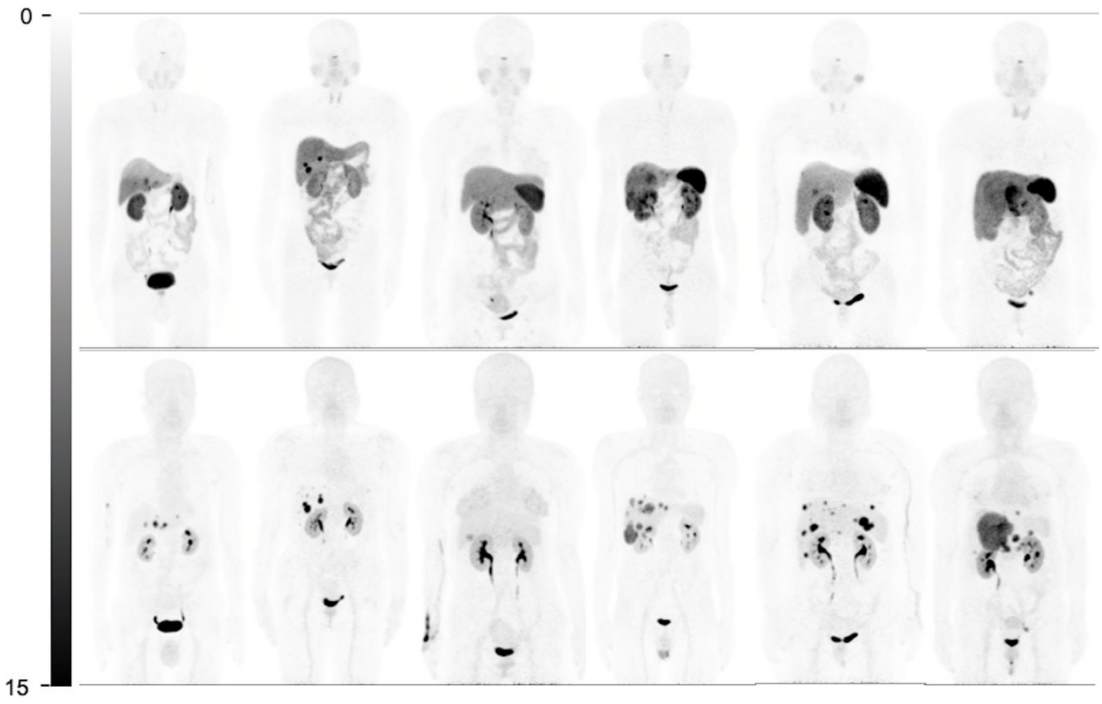

Figure 1. Comparison of whole-body maximum-intensity projection (MIP) images in 6 representative patients (Patient No. 7, 8, 11, 14, 27, and 29 from left to right). Physiological uptake is seen at pituitary gland, salivary glands, thyroids, adrenal glands, spleen (splenectomy in Patient 7 and 8), and bowel on ^{68}Ga-DOTATATE MIP images (upper row). Nevertheless, these normal organs show none or very mild uptake on ^{68}Ga-DOTA-JR11 MIP images (lower row). Besides, ^{68}Ga-DOTA-JR11 (lower row) depicts more liver lesions than ^{68}Ga-DOTATATE (upper row), with a lower liver background.

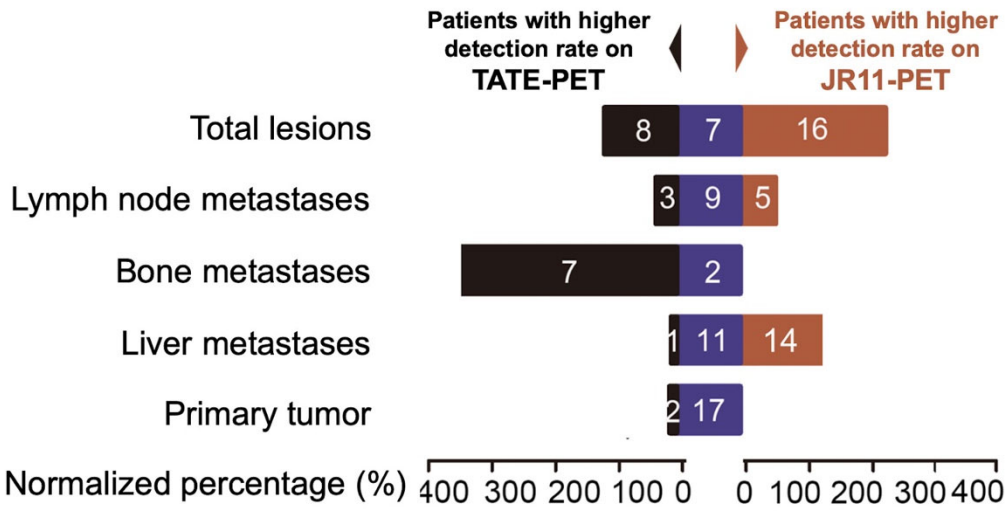

Figure 2. Patient-based comparison of lesions detection.

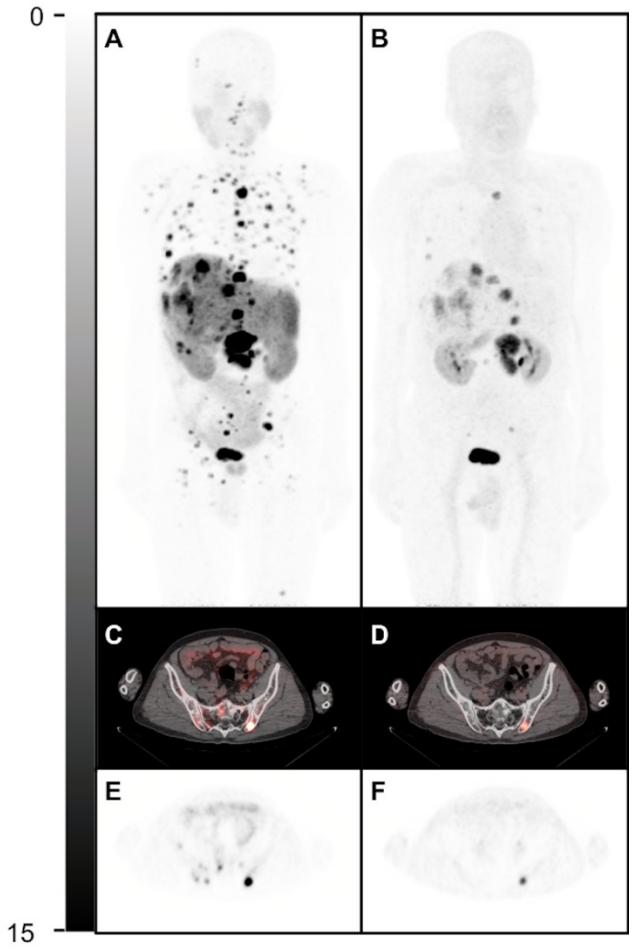

Figure 3. The PET/CT images of ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-JR11 in a patient (Patient No. 23) with pancreatic neuroendocrine tumor and multiple liver, lymph node, and bone metastases. ^{68}Ga-DOTATATE MIP image (A) shows much more bone lesions than ^{68}Ga-DOTA-JR11 (B), while the primary tumor, lymph node metastases, and liver metastases are comparable. Transaxial fusion (C) and PET images (E) of ^{68}Ga-DOTATATE show multiple bone lesions in the pelvic bone. Only one of them is positive with ^{68}Ga-DOTA-JR11 (fusion, D; PET, F).

Patient	Age	Gender	Primary tumor site	Biopsy site	Tumor grade	Ki67 value	Indication of imaging	Primary tumor resected
1	71	Female	Rectum	Rectum	G1	< 1%	Restaging	No
2	41	Male	CUP	Liver	G2	NA	Restaging	No
3	31	Female	Pancreas	Pancreas	G2	10%	Staging	No
4	33	Female	CUP	Humerus	G1	1%	Staging	No
5	50	Female	Pancreas	Liver	G1	2%	Staging	No
6	36	Male	Small intestine	Duodenum	G1	< 1%	Staging	No
7	69	Male	Pancreas	Pancreas	G2	10%	Restaging	Yes
8	49	Female	Pancreas	Pancreas	G2	5%	Restaging	Yes
9	42	Male	Multiple sites *	Pancreas	G2	10%	Restaging	No
10	69	Male	Pancreas	Liver	G2	10%	Restaging	No
11	42	Female	Pancreas	Liver	G2	3%	Restaging	No
12	53	Female	Rectum	Rectum	G2	5%	Staging	No
13	37	Female	Rectum	Rectum	G2	4%	Staging	no
14	37	Male	Pancreas	Liver	G2	4%	Staging	no
15	62	Female	Pancreas	Pancreas	G2	15%	Restaging	no
16	53	Female	Small intestine	Duodenum	G2	5%	Restaging	yes
17	43	Female	Small intestine	Liver	G2	6%	Staging	no
18	78	Female	CUP	Liver	G2	15%	Staging	no
19	57	Female	Pancreas	Pancreas	G1	2%	Restaging	yes
20	49	Female	Small intestine	Liver	G2	NA	Restaging	no
21	30	Male	Thymus	Thymus	G2	10%	Restaging	yes
22	50	Male	CUP	Liver	G2	5%	Staging	no
23	67	Male	Pancreas	Liver	G2	10%	Restaging	no
24	57	Female	Pancreas	Pancreas	G2	5%	Restaging	yes
25	43	Female	Stomach	Stomach	G2	10%	Restaging	yes

26	57	Male	Lung	Lung	G2	5%	Staging	no
27	60	Female	Pancreas	Pancreas	G2	8%	Staging	no
28	61	Male	Small intestine	Duodenum	G1	1%	Staging	no
29	59	Female	Rectum	Rectum	G2	5%	Restaging	yes
30	59	Male	Lung	Liver	G1	1%	Restaging	No
31	45	Female	CUP	Liver	G1	< 1%	Restaging	no

Supplemental Table 1. Patients' clinical characteristics

NA: not available

* Patient 14 was diagnosed as multiple endocrine neoplasia type 1, presenting with parathyroid adenoma and multiple neuroendocrine tumors in the stomach, duodenum, and pancreas.