Head-to-Head Comparison of ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET/CT in Patients with Metastatic, Well-Differentiated Neuroendocrine Tumors: Interim Analysis of a Prospective Bicenter Study

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The current study aimed to compare ^{68}Ga-NODAGA-Cpa-cyclo(D-Cys-amino-Phe-hydroorotic acid-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)-D-Tyr-NH_2 (JR11) and ^{68}Ga-DOTATATE PET/CT in patients with metastatic, well-differentiated neuroendocrine tumors. **Methods:** A prospective bicenter study aimed at enrolling 100 patients with histologically proven, metastatic or unresectable, well-differentiated neuroendocrine tumors was conducted. The first 48 patients represented the study cohort. Each patient received ^{68}Ga-DOTATATE on the first day and ^{68}Ga-NODAGA-JR11 on the second day. Whole-body PET/CT scans were performed at 40–60 min after injection. Normal-organ uptake, lesion numbers, lesion uptake, and sensitivity were compared. The potential impact on clinical management was also determined. **Results:** Overall, ^{68}Ga-NODAGA-JR11 demonstrated lower background uptake in normal organs. Compared with ^{68}Ga-DOTATATE, ^{68}Ga-NODAGA-JR11 detected significantly more liver lesions (673 vs. 584, $P = 0.002$). The target-to-background ratio of liver lesions was significantly higher on ^{68}Ga-NODAGA-JR11 (6.4 ± 8.7 vs. 3.1 ± 2.6, $P = 0.000$). Comparable uptake was observed for primary tumors, bone lesions, and lymph node metastases. In total, 180 lesions were detected on conventional imaging in 15 patients; 165 and 139 lesions of them were positive on ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE, leading to a sensitivity of 91.7% and 77.2%, respectively. In 14.5% (7/48) of patients, ^{68}Ga-NODAGA-JR11 PET might have a potential impact on clinical management. **Conclusion:** ^{68}Ga-NODAGA-JR11 shows better sensitivity and a higher target-to-background ratio than ^{68}Ga-DOTATATE. The detection of more lesions by the antagonist may have a potential impact on clinical management in a subgroup of patients.

Key Words: somatostatin receptor antagonist; ^{68}Ga-NODAGA-JR11; ^{68}Ga-DOTATATE; neuroendocrine tumor; PET/CT

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Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms arising from endocrine cells. Most NETs overexpress somatostatin receptor (SSTR), a G-protein–coupled membrane receptor that can be targeted for molecular imaging and radionuclide therapy (*1*). SSTR imaging plays a critical role in the management of NETs, including staging, restaging, prognosis, therapy decision-making, and response monitoring (*2*). However, the detection ability of ^{68}Ga-labeled SSTR agonists such as ^{68}Ga-DOTATATE is still limited. There remains a clinical need to improve SSTR imaging.

Recently, an important improvement in the field of SSTR imaging was the introduction of SSTR antagonists (*3–8*). Bass et al. described the first radiolabeled SSTR antagonists in 1996 (*9*). Cpa-cyclo(D-Cys-amino-Phe-hydroorotic acid-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)-D-Tyr-NH_2 (JR11) is a novel SSTR2 antagonist with promising results in preclinical studies, but the clinical evidence is scarce (*10*). We reported a case of ^{68}Ga-DOTATATE–negative gastric NET (grade 2). The gastric lesion was successfully imaged with ^{68}Ga-NODAGA-JR11 and subsequently treated with endoscopic submucosal dissection (*11*). Nicolas et al. found that ^{68}Ga-NODAGA-JR11 was superior to ^{68}Ga-DOTATOC in sensitivity, lesion detection, and image contrast in patients with low- or intermediate-grade gastroenteropancreatic NETs (*12*).

The current article describes an interim analysis of a prospective bicenter study aimed at comparing ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET/CT in patients with metastatic, well-differentiated NETs.

MATERIALS AND METHODS

Study Design and Patient Population

This was a prospective bicenter study conducted at the First Affiliated Hospital of Fujian Medical University and Peking Union Medical College Hospital and aimed to enroll 100 patients. The study was registered at ClinicalTrials.gov (NCT04897542) and approved by the institutional review board of the First Affiliated Hospital of Fujian Medical University and Peking Union Medical College Hospital. All subjects gave written informed consent before study participation. Patients with histologically proven, metastatic or unresectable, well-differentiated NETs (grade 1 or 2) were prospectively and consecutively recruited to this study. If the patient was on a long-acting somatostatin analog, a washout phase of 28 d was required before study participation. No NET-specific treatment was allowed between the 2 scans. This interim analysis comprises 48 patients enrolled between August 2020 and November 2021, 24 in each center.

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

Good-manufacturing-grade NODAGA-JR11 and DOTATATE precursors were supplied by CS Bio Co. and ABX GmbH, respectively. The radiolabeling was performed manually in a hot cell. Briefly, $^{68}GaCl_3$ was eluted from a $^{68}Ge/^{68}Ga$ generator (Eckert & Ziegler GalliaPharm) using 5 mL of 0.1 M hydrochloride acid. The eluent (about 250 MBq) was added to a reaction vial containing the precursor (for NODAGA-JR11, 40 μg; for DOTATATE, 40 μg) and dissolved in sodium acetate buffer, for a final pH of 4 for the reaction mixture. The mixture was heated to 100°C for 10 min. After cooling at room temperature, the reaction mixture was diluted with 5 mL of saline and then loaded onto an Oasis HLB cartridge (Waters) (preconditioned with 1 mL of ethanol and 5 mL of saline) and washed with saline to remove unincorporated radionuclide. Finally, the product was eluted off the cartridge with 75% ethanol solution, 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 more than 99%, and the ethanol amount was not more than 10% for injection. The non–decay-corrected radiochemical yield of ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE was about 65% for a 30-min radiolabeling process. The radioactivity of the final injection would be about 150 MBq after 40 min of ^{68}Ga elution (30 min for labeling + 10 min for patient preparation). The injected peptide dose was 40 μg per patient, and the specific activity was about 3.75 MBq/μg.

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

The study was performed on a time-of-flight PET/CT scanner (Biograph mCT64; Siemens) at both centers. The patients received an intravenous injection of ^{68}Ga-DOTATATE (150 ± 55 MBq) on the first day and ^{68}Ga-NODAGA-JR11 (148 ± 52 MBq) on the second day. The CT scans were performed with tube voltage of 120 kV, effective tube current of 70–120 mA (CareDose 4D; Siemens), and a slice thickness of 3 mm. PET data were reconstructed using ordered-subsets expectation maximization (2 iterations and 21 subsets).

Adverse Event Monitoring

Vital signs (blood pressure and heart rate) and clinical symptoms were monitored and recorded for up to 2 h after injection. Adverse events were recorded according to version 4.03 of the Common Terminology Criteria for Adverse Events.

Image Interpretation and Data Analysis

^{68}Ga-DOTATATE and ^{68}Ga-NODAGA-JR11 PET/CT images were analyzed on a Syngo MultiModality Workplace (Siemens). The images were reviewed by a board-certified nuclear medicine physician. The reader was masked to patients' medical history and radiopharmaceutical. When the reader reviewed the images, the lesion number, location, and uptake were recorded in the report form. After all measurements were finished, the reader was permitted to reopen the 2 scans again and compare the data. However, any revision to the original data was not allowed in this phase; only comparison and reconciliation were allowed.

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

Any focal accumulation of ^{68}Ga-DOTATATE and ^{68}Ga-NODAGA-JR11 not explained by physiologic uptake or benign lesions, such as bone trauma, hemangioma, and degeneration disease, was defined as a focal lesion. CT correlation was used to help characterize the lesions. Regions of interest were drawn around the lesions on transverse slices for semiquantitative analysis. The number and SUV_{max} of focal lesions were recorded. For liver lesions, relative uptake was quantified using target-to-background ratio, defined as the SUV_{max} of the lesion divided by the SUV_{max} of the normal liver parenchyma.

Sensitivity

To calculate the sensitivity of ^{68}Ga-DOTATATE and ^{68}Ga-NODAGA-JR11 PET/CT, comparison with conventional imaging using contrast-enhanced MRI or CT was performed. Patients with available conventional imaging (MRI was preferred if both MRI and CT were available) within 1 y of the PET study were included in the analysis.

The lesion-based sensitivity of the PET studies was calculated as the percentage of lesions on conventional imaging positive for PET uptake. An alternative combination strategy was also used to calculate the sensitivity; that is, lesions visible on any of the 3 imaging modalities (conventional imaging, ^{68}Ga-DOTATATE PET, or ^{68}Ga-NODAGA-JR11 PET) were considered true lesions for NET. This was part of an exploratory extension and not part of the original study design.

Potential Impact on Clinical Management

To answer whether the imaging findings on ^{68}Ga-NODAGA-JR11 PET/CT would change the patients' clinical management, an imaging-based post hoc analysis was done. The ^{68}Ga-NODAGA-JR11 PET results would be considered to potentially impact clinical management if any of the criteria shown in Table 1 were fulfilled. This was part of an exploratory extension and not part of the original study design.

Statistical Analysis

Data were expressed as mean ± SD. Differences in SUV_{max} and target-to-background ratio between ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE were evaluated using paired *t* tests (SPSS, version 23) and only for matched lesions. The lesion numbers were statistically compared using sign tests. The McNemar test was used to compare sensitivity. A *P* value of less than 0.05 was considered to indicate a significant difference.

TABLE 1
Criteria to Define Potential Impact on Clinical Management of ^{68}Ga-NODAGA-JR11 over ^{68}Ga-DOTATATE

Lesion type	Imaging finding
Primary	Not found → found
Liver metastases	Not found → found
	Unilobar lesions → bilobar lesions*
	No more than 5 lesions → more than 5 lesions†
Bone metastases	Not found → found
	Oligometastases (no more than 3 lesions) → more than 3 lesions‡
Nodal metastases	Not found → found
Other metastases	Not found → found

*Finding of bilobar lesions could affect decision on and delivery of surgery.

†Number of lesions could affect decision on ablation.

‡Number of lesions could affect decision on external-beam radiation therapy.

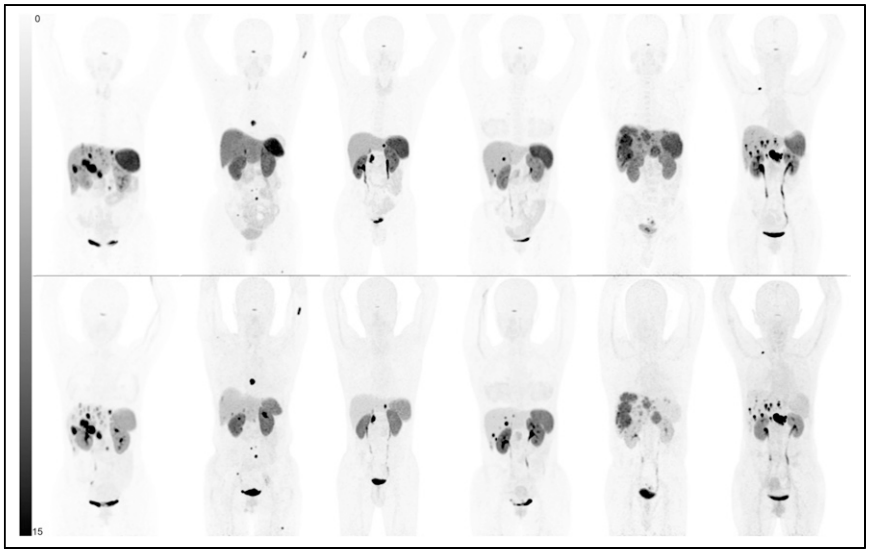


FIGURE 1. Comparison of whole-body maximum-intensity projections of 6 representative patients (patients 26, 32, 33, 36, 43, and 45 from left to right). Physiologic uptake is seen at pituitary gland, salivary glands, thyroids, adrenal glands, spleen, and bowel on ^{68}Ga-DOTATATE images (top row). Nevertheless, these normal organs show minimal or mild uptake on ^{68}Ga-NODAGA-JR11 images (bottom row). Besides, ^{68}Ga-NODAGA-JR11 depicts more liver lesions than ^{68}Ga-DOTATATE, with lower liver background uptake.

RESULTS

The clinical characteristics are summarized in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). Both tracers were tolerated well by all patients. No adverse events were reported.

Biodistribution

Mild to moderate uptake was noted for ^{68}Ga-NODAGA-JR11 in almost all organs except the urinary tract (Fig. 1; Table 2). Compared with ^{68}Ga-DOTATATE, ^{68}Ga-NODAGA-JR11 showed lower background uptake except for the lung.

Tumor Detection

In total, 1,095 and 1,003 focal lesions were depicted on ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET/CT, respectively ($P = 0.007$; Supplemental Table 2).

On patient-based comparison, ^{68}Ga-NODAGA-JR11 demonstrated a better detection ability for liver lesions (Fig. 1). Of 37 patients with liver metastases, 54.1% (20/37) showed more liver metastases on ^{68}Ga-NODAGA-JR11 than on ^{68}Ga-DOTATATE, whereas 35.1% (13/37) demonstrated comparable results. Only 4 patients had fewer liver lesions detected on ^{68}Ga-NODAGA-JR11 PET/CT (Fig. 2).

On lesion-based comparison, ^{68}Ga-NODAGA-JR11 detected significantly more liver lesions (673 vs. 584, $P = 0.002$; Fig. 3).

For primary tumors, bone metastases, and lymph node metastases, the 2 tracers were comparable on both patient-based and lesion-based comparison.

Tumor Uptake

For matched lesions, ^{68}Ga-NODAGA-JR11 demonstrated comparable uptake except that uptake by bone lesions was significantly lower (Table 3). The target-to-background ratio for liver lesions, however, was significantly higher on ^{68}Ga-NODAGA-JR11 than on ^{68}Ga-DOTATATE (6.4 ± 8.7 vs. 3.1 ± 2.6, $P = 0.000$).

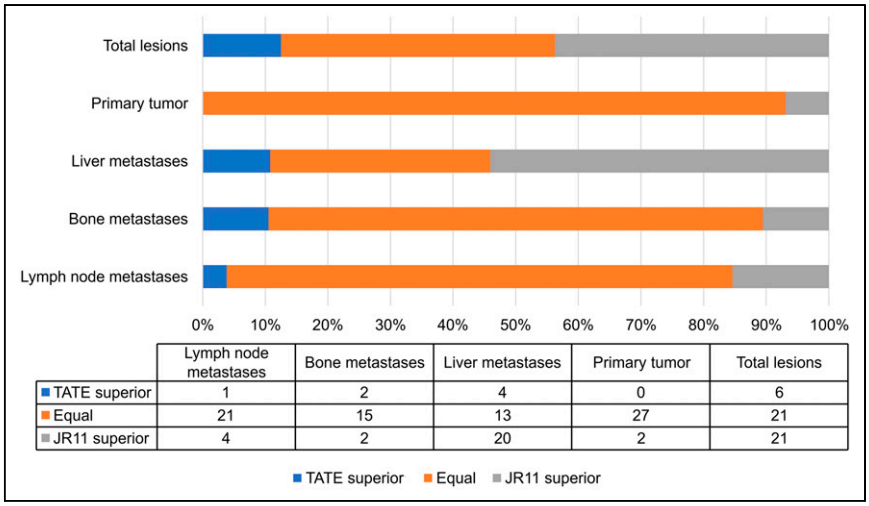
Sensitivity Estimation

There were 15 patients (6 from one center and 9 from the other) with available contrast-enhanced MRI or CT within 1 y of the study. The median interval between PET and conventional imaging was 3 mo (range, 0–12 mo). Eight of the follow-up conventional imaging studies were contrast-enhanced MRI, and 7 were contrast-enhanced CT. There were a total of 180 lesions detected

TABLE 2
Comparison of Normal-Organ SUV_{max} Between ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET/CT

Organ	JR11	TATE	*P*
Spleen ($n = 43$)*	8.4 ± 4.2	17.7 ± 5.5	0.000
Renal cortex ($n = 48$)	10.2 ± 3.2	11.9 ± 2.8	0.006
Adrenal glands ($n = 48$)	7.1 ± 3.7	11.8 ± 4.5	0.000
Pituitary gland ($n = 48$)	5.7 ± 2.8	7.8 ± 3.0	0.000
Stomach wall ($n = 48$)	1.4 ± 0.6	1.9 ± 1.0	0.002
Lung ($n = 48$)	0.5 ± 0.2	0.3 ± 0.1	0.000
Normal liver parenchyma ($n = 48$)	3.9 ± 1.9	7.1 ± 2.0	0.000
Small intestine ($n = 48$)	1.7 ± 0.7	2.5 ± 1.3	0.001
Pancreas (uncinate process, $n = 41$)†	3.3 ± 2.2	4.7 ± 2.5	0.008
Bone marrow (L5 vertebra, $n = 45$)‡	1.2 ± 0.4	1.5 ± 0.4	0.000

*Splenectomy was done in 5 patients.
†Pancreas uptake measurement was ruled out in 7 patients because of focal lesions in uncinate process or partial or total pancreatectomy.
‡Bone marrow uptake for focal lesions in L5 vertebra could not be measured in 3 patients.
Data are expressed as mean ± SD.



	Lymph node metastases	Bone metastases	Liver metastases	Primary tumor	Total lesions
TATE superior	1	2	4	0	6
Equal	21	15	13	27	21
JR11 superior	4	2	20	2	21

FIGURE 2. Patient-based comparison of lesion detection.

on conventional imaging; 165 and 139 of the lesions were positive on ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE, leading to a mean sensitivity of 91.7% (range, 87.6%–95.7%) and 77.2% (range, 71.0%–83.4%), respectively. All lesions missed by ^{68}Ga-NODAGA-JR11 were small, usually less than 0.5 cm. Bone and other lesions outside the scan field of view on conventional imaging were not included in the analysis.

Notably, 26 lesions within the scan field of view on conventional imaging were identifiable on PET but not on conventional imaging. All were positive for uptake on both PET scans, including 1 pancreatic lesion missed on MRI, 1 pancreatic lesion missed on CT, and 24 hepatic lesions missed on CT. All 26 lesions were in locations typical of NET and had a markedly elevated SUV_{max} (mean, 21.5 and 18.7 for ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE, respectively). After discussion with a radiologist and an oncologist, these 26 lesions were all considered NET lesions. There were 206 lesions identified using the combination strategy. The sensitivity of ^{68}Ga-NODAGA-JR11, ^{68}Ga-DOTATATE, and conventional imaging was 92.7% (range, 89.1%–96.3%), 79.6% (range, 74.1%–85.2%), and 87.4% (range, 82.8%–92.0%), respectively.

Potential Impact on Clinical Management

In 56% (27/48) of patients, there were discrepancies between ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET. Among them, 14.5% (7/48) of patients showed that ^{68}Ga-NODAGA-JR11 PET might have potentially changed clinical management by detecting more lesions than ^{68}Ga-DOTATATE according to the criteria. In 1 patient (patient 41), ^{68}Ga-NODAGA-JR11 revealed fewer liver lesions on PET than did ^{68}Ga-DOTATATE, a finding that could lead to insufficient management if standard ^{68}Ga-DOTATATE PET were omitted. In the remaining 19 patients, the discrepancies were not significant enough to change clinical management (Table 4).

DISCUSSION

Our study prospectively compared lesion detection ability between ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE in a single group of patients. The strengths of the study include a prospective, bicenter design and a large cohort. The results favor ^{68}Ga-NODAGA-JR11 because of a higher detection ability and better image contrast for liver metastases, as well as a potential impact on clinical management.

Despite lack of tracer internalization into tumor cells, preclinical and initial clinical studies have facilitated a shift from SSTR agonists to antagonists in recent years (*3–5,13,14*). In our previous study, the antagonist ^{68}Ga-DOTA-JR11 showed an overall lesion detection ability comparable to that of ^{68}Ga-DOTATATE and lower uptake (*13*). This finding contrasts somewhat with the present findings. In the current study, ^{68}Ga-NODAGA-JR11 showed a higher lesion detection ability and comparable tumor uptake. The divergence might be explained by the different SSTR2 affinity (50% inhibitory concentrations of 29, 1.2, and 0.2 nmol/L for ^{68}Ga-DOTA-JR11, ^{68}Ga-NODAGA-JR11, and ^{68}Ga-DOTATATE, respectively) (*15*).

In addition, we did notice a statistically significant difference in bone lesion uptake between ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET/CT. The difference, however, was small and did not affect the detection of bone lesions by ^{68}Ga-NODAGA-JR11. It can in part be explained

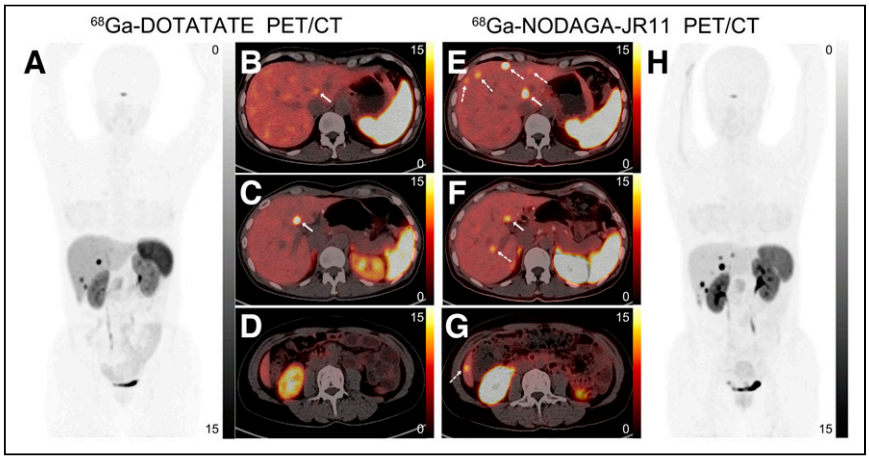


FIGURE 3. Lesion-based comparison of lesion detection. ^{68}Ga-DOTATATE and ^{68}Ga-NODAGA-JR11 PET/CT images are shown of postoperative gastric NET patient (patient 36) with multiple liver metastases. (A) ^{68}Ga-DOTATATE maximum-intensity projection shows several liver lesions with high uptake. (B) Transaxial fusion image appears to show abnormal moderate-uptake lesion (arrow) in high liver background uptake. (C and D) One transaxial fusion image (C) shows liver metastasis (arrow), whereas no liver lesion was found in another (D). (H) ^{68}Ga-NODAGA-JR11 maximum-intensity projection shows many more liver lesions than ^{68}Ga-DOTATATE. (E–G) Transaxial fusion images at same 3 levels as in B–D similarly found liver lesions that matched those on ^{68}Ga-DOTATATE (solid arrows). ^{68}Ga-NODAGA-JR11 PET/CT shows lower liver background uptake and additional liver metastases (dashed arrows) at sites that were negative on ^{68}Ga-DOTATATE PET/CT.

TABLE 3
Uptake of Matched Lesions on ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET/CT

Parameter	JR11	TATE	*P*
SUV_{max}			
Primary tumor (n = 40)	24.7 ± 20.9	23.5 ± 20.1	0.64
Liver metastases (n = 576)	18.0 ± 17.3	18.0 ± 13.5	0.630
Bone metastases (n = 237)	8.5 ± 6.7	10.1 ± 7.8	0.000
Lymph node metastases (n = 87)	16.0 ± 16.0	15.7 ± 16.4	0.725
Pleural or peritoneal metastases (n = 11)	4.4 ± 2.4	4.9 ± 3.1	0.205
Tumor-to-background ratio for liver metastases (n = 569)	6.4 ± 8.7	3.1 ± 2.6	0.000

Data are expressed as mean ± SD.

by the low bone marrow uptake of ^{68}Ga-NODAGA-JR11. Therefore, we do not think the difference is marked enough to generate clinical implications.

We observed that the bone marrow uptake of ^{68}Ga-NODAGA-JR11 was lower than that of ^{68}Ga-DOTATATE. This finding somewhat contradicts already published literature showing potentially increased hematologic toxicity with the therapeutic counterpart (^{177}Lu-DOTA-JR11) in comparison to ^{177}Lu-DOTATATE (*16*). The underlying mechanism of the hematologic toxicity of antagonist peptide receptor radionuclide therapy is currently not well understood. Bone marrow uptake is low using either a ^{68}Ga- or a ^{177}Lu-antagonist. The reason should not be the radiation to the general bone marrow, which was considered the main reason for radioactive hematologic toxicity. We agree with Reidy-Lagunes et al. that antagonists might be able to target SSTR expressed on bone marrow stem cells or progenitor cells, causing more severe and prolonged bone marrow suppression (*16*).

^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE have a sensitivity of 91.7% (range, 87.6%–95.7%) and 77.2% (range, 71.0%–83.4%), respectively, using conventional imaging as a reference. Nevertheless, whereas dedicated contrast-enhanced MRI might be the best imaging modality for the detection of liver metastasis, conventional imaging may not serve as the perfect reference for whole-body SSTR PET imaging (*17,18*). That is to say, conventional imaging—contrast-enhanced CT in particular—is not sensitive enough for NET detection. Some SSTR-positive lesions observed on PET might not be visualized on conventional imaging (*19*). This is especially true for bone lesions, which are usually out of the scan field of view; nonosseous changing soft-tissue lesions that are embedded in surrounding soft tissues; and lymph nodes that are too small to fit the size criteria. This hypothesis was supported by our observation that ^{68}Ga-NODAGA-JR11 had higher sensitivity than conventional imaging using a combination strategy. However, we must emphasize the importance of the modality chosen as the standard of truth. Of the 26 lesions missed on conventional imaging, 25 were missed by conventional CT. The results could be different if only MRI is involved.

TABLE 4
Potential Impact on Clinical Management of ^{68}Ga-NODAGA-JR11 PET/CT Imaging

Patient no.	Imaging finding
10	Liver: unilobar lesions → bilobar lesions
	Bone: not found → found
12	Liver: unilobar lesion → bilobar lesions
18	Primary: not found → found
	Liver: not found → found
23	Lymph node: not found → found
32	Liver: not found → found
	Lymph node: not found → found
	Other metastases: not found→found (pancreatic metastasis from rectal NET)
37	Liver: unilobar lesion → bilobar lesions
41*	Liver: bilobar lesions → unilobar lesions
48	Liver: not found → found

*Bilobar liver diseases on ^{68}Ga-DOTATATE but unilobar diseases on ^{68}Ga-NODAGA-JR11.

The potential impact of antagonist PET on clinical management is essential for clinicians to know but has not been previously reported. Our post hoc analysis showed, in a subgroup (14.5%) of patients, that detection of more lesions by ^{68}Ga-NODAGA-JR11 could have a potential impact on the patients' clinical management. The ability to detect more liver metastases with antagonists may also change the therapeutic strategy if local therapy for hepatic lesions were to be considered. Partial liver resection would be contraindicated if additional bilobar liver lesions are identified (*20*). Besides, the lower background uptake of ^{68}Ga-NODAGA-JR11 also helps to differentiate between physiologic uptake and true lesions. The intrapancreatic accessory spleen is a congenital entity often incidentally detected by imaging and can be misdiagnosed as NET. High uptake of ^{111}In-diethylenetriamine pentaacetate octreotide and ^{68}Ga-DOTATATE in the intrapancreatic accessory spleen has been described in some case reports, making it an important pitfall of agonist imaging (*21,22*). Compared with ^{68}Ga-DOTATATE, ^{68}Ga-NODAGA-JR11 had much lower spleen uptake. The intrapancreatic accessory spleen tends to have uptake comparable to or lower than that in the spleen parenchyma on ^{68}Ga-NODAGA-JR11 PET/CT, whereas well-differentiated NET tends to have higher uptake than in the spleen (Supplemental Fig. 1). In that sense, antagonist imaging might provide a novel strategy to distinguish NET from an intrapancreatic accessory spleen.

The advantage of antagonists lies not only in better imaging of NETs but also in treatment decision-making. As a diagnostic companion for ^{177}Lu-DOTA-JR11, ^{68}Ga-NODAGA-JR11 is essential to decide whether patients are eligible for peptide receptor radionuclide

therapy with ^{177}Lu-DOTA-JR11. In the phase I trial of ^{177}Lu-DOTA-JR11, the overall response rate was 45% (9/20 patients) after only 2 cycles of treatment (*16*). In particular, peptide receptor radionuclide therapy with antagonists might be a better choice in patients with agonist-negative but antagonist-positive lesions (*20*). Zhang et al. provided preliminary evidence of efficacy using ^{177}Lu-DOTA-LM3 treatment in a patient with ^{68}Ga-DOTATOC–negative high-grade liver metastases (*23*). The patient had a nearly complete remission after 3 cycles of peptide receptor radionuclide therapy, with a total of 20.4 GBq of ^{177}Lu-DOTA-LM3. Besides, higher tumor uptake and prolonged retention of ^{68}Ga-NODAGA-JR11 may result in favorable tumor-to-organ ratios and thus be an advantage for therapy with SSTR2 antagonists, even if all the lesions are visible on SSTR2 agonist PET/CT imaging.

Our study had some limitations. A crossover design to reduce the impact of the sequence of the 2 PET studies could further strengthen our study. Because of the nature of post hoc analysis, the sensitivity calculation was limited by the small population. The image files of some patients were not available and thus could not be analyzed. Furthermore, the comparison was limited to the scan field of view of conventional imaging, and lesions outside this field, such as bone metastases, were not included in the analysis. In addition, the potential impact of ^{68}Ga-NODAGA-JR11 PET on clinical management was analyzed using imaging-based criteria. The clinician's opinion should also be included in future studies.

CONCLUSION

^{68}Ga-NODAGA-JR11 shows better sensitivity and a higher target-to-background ratio than ^{68}Ga-DOTATATE. The detection of more lesions by antagonists has a potential impact on clinical management in a subgroup of patients.

DISCLOSURE

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KEY POINTS

QUESTION: Is PET/CT with the SSTR antagonist ^{68}Ga-NODAGA-JR11 more efficient at detecting lesions than the agonist ^{68}Ga-DOTATATE in patients with metastatic, well-differentiated NETs?

PERTINENT FINDINGS: Forty-eight patients with metastatic, well-differentiated NETs were prospectively enrolled in a bicenter study to compare lesion detection ability between ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTATATE PET/CT. ^{68}Ga-NODAGA-JR11 was better able to detect liver metastases and had a higher target-to-background ratio than ^{68}Ga-DOTATATE.

IMPLICATIONS FOR PATIENT CARE: The new radiopharmaceutical ^{68}Ga-NODAGA-JR11 is more valuable than SSTR agonists in patients with NETs, especially in patients with liver-dominant metastases.

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