Safety and Efficacy of ^{68}Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors

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Our purpose was to evaluate the safety and efficacy of ^{68}Ga-DOTATATE PET/CT compared with ^{111}In-pentetreotide imaging for diagnosis, staging, and restaging of pulmonary and gastroenteropancreatic neuroendocrine tumors. **Methods:** ^{68}Ga-DOTATATE PET/CT and ^{111}In-pentetreotide scans were obtained for 78 of 97 consecutively enrolled patients with known or suspected pulmonary or gastroenteropancreatic neuroendocrine tumors. Safety and toxicity were measured by comparing vital signs, serum chemistry values, or acquisition-related medical complications before and after ^{68}Ga-DOTATATE injection. Added value was determined by changes in treatment plan when ^{68}Ga-DOTATATE PET/CT results were added to all prior imaging, including ^{111}In-pentetreotide. Interobserver reproducibility of ^{68}Ga-DOTATATE PET/CT scan interpretation was measured between blinded and nonblinded interpreters. **Results:** ^{68}Ga-DOTATATE PET/CT and ^{111}In-pentetreotide scans were significantly different in impact on treatment ($P < 0.001$). ^{68}Ga-DOTATATE PET/CT combined with CT or liver MRI changed care in 28 of 78 (36%) patients. Interobserver agreement between blinded and nonblinded interpreters was high. No participant had a trial-related event requiring treatment. Mild, transient events were tachycardia in 1, alanine transaminase elevation in 1, and hyperglycemia in 2 participants. No clinically significant arrhythmias occurred. ^{68}Ga-DOTATATE PET/CT correctly identified 3 patients for peptide-receptor radiotherapy incorrectly classified by ^{111}In-pentetreotide. **Conclusion:** ^{68}Ga-DOTATATE PET/CT was equivalent or superior to ^{111}In-pentetreotide imaging in all 78 patients. No adverse events requiring treatment were observed. ^{68}Ga-DOTATATE PET/CT changed treatment in 36% of participants. Given the lack of significant toxicity, lower radiation exposure, and improved accuracy compared with ^{111}In-pentetreotide, ^{68}Ga-DOTATATE imaging should be used instead of ^{111}In-pentetreotide imaging where available.

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Neuroendocrine tumors (NETs) are usually slow-growing malignancies, mostly of the respiratory and digestive tracts, that cause significant morbidity and mortality (*1*). Although generally considered rare because of low incidence of 2.5–5/100,000 in the United States, NETs have a higher prevalence (112,000 cases) than more aggressive and common malignancies, such as pancreatic or gastric adenocarcinoma (*2*). NETs can be difficult to diagnose because of protean clinical presentations. Common chronic symptoms include cough or diarrhea, whereas others are clinically silent. The average time from symptom onset to diagnosis can be up to 9 y (*3*). Despite its reputation as a relatively benign disease, NETs are highly metastatic, with most bronchopulmonary and small intestinal cases presenting with metastatic disease (*4*). NETs have many treatment options, which differ significantly from adenocarcinomas. Surgery is the primary treatment with the best opportunity for cure and can also mitigate tumor/hormone load from metastatic burden (*5*). Other treatments include systemic therapy with somatostatin analogs, biologics, molecularly targeted therapies, peptide-receptor radionuclide therapy (PRRT), liver-directed therapy, and platinum-doublet chemotherapy (*6–11*).

Given the range of treatments, it is critical to accurately delineate the extent of disease for proper management. Imaging plays an essential role in staging by showing local extent and distant disease. Conventional imaging, such as CT and MRI, provides critical information but is limited in its field of view and is highly dependent on protocol choice (*12–15*). Functional imaging with radiopharmaceuticals is an important diagnostic tool because most NETs have high cell surface somatostatin receptor expression levels (*16*). Using somatostatin analogs conjugated to ^{111}In allows

whole-body imaging with planar or SPECT, or SPECT/CT (*17*), the gold-standard for NET imaging for more than 2 decades (*18,19*). However, PET/CT, developed in this interim, has higher resolution than SPECT. In oncology, ^{18}F-FDG PET/CT is the imaging reference for most malignancies. Outside the United States, PET/CT with somatostatin analogs conjugated to the positron-emitting radioisotope ^{68}Ga is rapidly replacing ^{111}In-pentetreotide imaging (*20–23*).

The purpose of this study was to evaluate toxicity related to administration of ^{68}Ga-DOTATATE, a somatostatin analog with near-exclusive and high-affinity binding to somatostatin receptor subtype 2A (*24*) and to compare the incremental value of ^{68}Ga-DOTATATE compared with ^{111}In-pentetreotide imaging.

MATERIALS AND METHODS

Patient Population

This study is investigator-initiated with extramural (VA Merit Review I01BX007080, Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network, and Vanderbilt Institute for Clinical and Translational Research grant support [UL1 TR000445 from NCATS/NIH]) and local philanthropic and institutional support and is a registered U.S. clinical trial (NCT01396382). Neuroendocrine cancer is a designated orphan disease, and ^{68}Ga-DOTATATE is a designated orphan drug, by the U.S. Food and Drug Administration. In this study of 98 ^{68}Ga-DOTATATE PET/CT scans obtained for 97 consecutively enrolled patients between March 2011 and November 2013, 90 having a proven diagnosis of NET, prospective analysis of safety and toxicity data and ^{68}Ga-DOTATATE scan findings was performed. Informed consent was obtained for all subjects, with local institutional review board approval and oversight (Vanderbilt University Medical Center IRB#110588) and U. S. Food and Drug Administration investigational new drug approval (IND 111972). The initial 2 patients were scanned with individual compassionate-use investigational new drugs using identical compounding. Standard-of-care imaging included ^{111}In-pentetreotide imaging (n = 87), diagnostic CT (n = 91), and MRI of the liver (n = 60). Participants were excluded from comparison of ^{68}Ga-DOTATATE with ^{111}In-pentetreotide scanning if no prior ^{111}In-pentetreotide scan was available, no ^{111}In-pentetreotide scan was available after a major surgical intervention occurring between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans, or if the time between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans exceeded 3 y. Safety and toxicity were assessed with preinjection and postimaging vital signs, pulse oximetry on room air, 12-lead electrocardiographs, and blood laboratory tests, including tumor markers, liver and renal functions, and blood counts, and direct patient questioning.

Imaging Protocol

Local synthesis of individual doses of ^{68}Ga-DOTATATE was performed as previously described. Radiation exposure to the patient is less than that from comparable ^{111}In-pentetreotide or ^{18}F-FDG PET/CT scans (*25*). No special dietary or activity restrictions were needed because ^{68}Ga-DOTATATE binds almost exclusively to somatostatin receptor 2A, which is not influenced by diet or activity (*26*). The mass of injected ^{68}Ga-DOTATATE peptide was 50 μg or less. Long-acting somatostatin analog medications are useful for symptomatic control and for antiproliferative therapy of NETs. Thus, patients on long-acting somatostatin analog medications (n = 51) did not stop these medications before undergoing ^{68}Ga-DOTATATE PET/CT.

Imaging was performed with an 8-slice Discovery STE PET/CT full-ring integrated scanner (GE Healthcare), beginning 65 min (range, 55–93 min) after injection. Immediately after patients emptied their urinary bladders, low-dose CT was performed from skull vertex to mid thighs for attenuation correction and anatomic localization. Emission imaging (3-dimensional mode, 4 min per bed) was then performed from mid thighs to skull vertex, with attenuation correction performed with the manufacturer's workstations and software. Total time from injection to scan completion was less than 2 h. CT reconstruction used filtered backprojection, with emission image reconstruction via ordered-subset expectation maximization iterative reconstruction, 2 iterations, with correction for scatter and randoms as previously reported (*25*).

Image Analysis

Many of our patients were not from our local area and brought conventional (CT, MRI) and ^{111}In-pentetreotide imaging results from outside facilities with them in digital format. All outside images and original reports were loaded onto the Vanderbilt University Medical Center's PACS linked to the Vanderbilt electronic health care records of each patient.

Because it was neither feasible nor ethical to obtain histologic confirmation of all sites of apparent metastatic tumor, diagnosis and impact on care for ^{68}Ga-DOTATATE versus ^{111}In-pentetreotide imaging was analyzed on a per-patient, not a per-lesion, basis. The diagnosis and scoring for the extent of disease was determined using a combination of the preponderance of evidence from conventional imaging and pathologic specimens before ^{68}Ga-DOTATATE imaging and then adding ^{68}Ga-DOTATATE scan results to the full clinical assessment of the patient using all available prior imaging and clinical information, to determine whether the addition of the ^{68}Ga-DOTATATE scan changed the treatment plan. Evidence for tumor was scored on the basis of original reports from conventional imaging as well as abnormal, especially focal, areas of uptake on ^{111}In-pentetreotide or ^{68}Ga-DOTATATE imaging. Scan results from the 3 independent ^{68}Ga-DOTATATE interpreters were entered into a spreadsheet, along with the original reports on conventional and ^{111}In-pentetreotide imaging, and then analyzed for the presence or absence of tumor, tumor improved, and stable or progressive disease compared with earlier scans, and whether, and how, the results of the ^{68}Ga-DOTATATE PET/CT scan changed patient management compared with either ^{111}In-pentetreotide alone or in combination with CT or MRI. Changes in management decision were determined and recorded via consensus of a weekly multidisciplinary NET board reviewing relevant imaging and clinical information. Contingency tables were generated with sensitivity and specificity, with confidence intervals estimated by exact binomial method. Differences in diagnostic test results were measured by McNemar χ^2 test and by comparison of receiver-operator curves for differences of diagnostic test accuracy.

Original clinical reports of ^{111}In-pentetreotide, CT, and MRI examinations were used for analysis of these examinations even if, in retrospect, additional sites of tumor were seen after comparison to ^{68}Ga-DOTATATE images. ^{68}Ga-DOTATATE imaging was interpreted via 2 methods. First, a physician board-certified in diagnostic radiology and nuclear medicine interpreted the ^{68}Ga-DOTATATE PET/CT, with full access to all prior imaging and clinical information. To avoid bias and to access interobserver reproducibility, 2 board-certified nuclear medicine physicians independently interpreted the ^{68}Ga-DOTATATE scans, blinded to all information, including other imaging, beyond knowing that the patient met enrollment criteria. The 2 blinded interpretations were recorded on a regional basis (solid organ, regional nodal, regional extranodal abdominal and pelvic involvement, extraabdominal/pelvic nodal or soft-tissue, and skeletal disease) sufficient to stage the patient's extent of disease relative to presence of tumor, resectability/extent of tumor, and intensity/presence of somatostatin receptor expression. Reviewer agreement was assessed by Fleiss κ and confidence interval estimated using the bootstrap method. The 3 physicians involved with ^{68}Ga-DOTATATE scan interpretation each have 30 or more y of experience in medical imaging and 10 or more y of experience in PET/CT interpretation.

Separately, a board-certified oncologic surgeon assessed the impact on care by comparing the intended treatment before and after the

^{68}Ga-DOTATATE scan, on a per-patient basis. The initial treatment plan was formulated using all available clinical, pathologic, and imaging information, including ^{111}In-pentetreotide scans. This treatment plan was then reviewed after adding the information from the ^{68}Ga-DOTATATE scan. Minor impact in treatment was characterized by a change within a treatment modality (intermodality), such as change in plan for already planned surgery or dosage adjustment of current medications. Major impact on treatment was characterized by a change of treatment modality (intramodality). Controversial cases, especially for major changes in management, were referred to the previously mentioned multidisciplinary NET tumor board. The addition of PRRT where previously not indicated, adding or discontinuing medications, or cancellation of surgery because of evidence of greater extent of disease on the ^{68}Ga-DOTATATE scan are examples of major, intramodality treatment changes.

Data Analysis

Toxicity data were compiled, and individual patient test results before and after scanning were compared. Blood laboratory test values included some fasting and nonfasting results as fasting status was not recorded. The cohorts' pre- and postscan test mean, median, standard errors, and interquartile ranges are reported in Supplemental Appendix 1 (supplemental materials are available at http://jnm.snmjournals.org). Statistically significant differences in test values were assessed by paired *t* test and the nonparametric Wilcoxon rank-sum test. All tests were 2-sided and performed using Stata (StataCorp.). Harm was measured by the Common Toxicity Criteria (version 1) of the National Cancer Institute (http://www.accessdata.fda.gov/scripts/cder/onctools/toxcrit1.cfm), with blood laboratory test values within the reference range having a harm level of 0. All participants were included for toxicity measurement.

RESULTS

Toxicity/Safety

No serious adverse events occurred among the 97 participants. Additional comorbidities influencing abnormal baseline, preinjection electrocardiograms included various conduction defects, 1 patient with electrocardiogram evidence of a prior anteroseptal infarction with a left anterior fascicular block, 2 patients with T-wave inversions, 2 patients with nonspecific ST-T wave changes, 2 patients with first degree AV block, 2 patients with p-wave abnormities, 1 patient with a ventricular paced rhythm, and 1 patient with a prior cardiac transplant. No serious arrhythmias, changes in

TABLE 1
Participant Demographics of Patients with Comparable Scans

Characteristic	All patients enrolled (*n* = 97)	^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans (*n* = 78)
Sex, female (%)	56 (58)	49 (63)
Mean age ± SD (y)	53.7 ± 11	53.4 ± 11
NET type (%)		
Midgut carcinoid	44 (45)	37 (47)
Gastroenteropancreatic	22 (23)	18 (23)
Unknown primary	12 (12)	7 (9)
Symptoms only	7 (7)	7 (9)
Pulmonary	7 (7)	5 (6)
Hindgut or rectal	3 (3)	3 (4)
Other	2 (2)	1 (1)
^{111}In-pentetreotide scan type		
Planar	5	3
Planar + SPECT	30	26
Planar + SPECT/CT	50	48
Outside scan, type not specified	12	1
Days between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans		
0–90	16	16
91–180	26	23
>180 d	56	39
Ki-67 category		
Low	24	19
Intermediate	37	29
High	6	4
Missing	30	26

Data in parentheses are percentages.

Q-T interval, or other significant changes from baseline were observed.

Minor adverse events occurred in 3 patients. One had minor itching the day after the ^{68}Ga-DOTATATE injection at the injection site, spontaneously resolving. One patient had an unexplained drop in postscan oxygen saturation on room air (before injection, 98%; after scanning, 90%), spontaneously resolving. One patient with a baseline heart rate of 87 had postscan tachycardia of 112, asymptomatic, spontaneously returning to less than 100 beats per minute within an hour. Other patients had minor and transient changes in laboratory tests, all asymptomatic. Elevated glucose was observed in 2 patients (both on long-acting somatostatin analog medication, known to cause glucose intolerance in up to 25% of patients; 1 of these 2 patients is a diabetic). Postscan fasting glucose plasma levels could not be consistently obtained after the participants returned home, so these 2 elevated values may not have been fasting. Changes in plasma levels of some blood markers were not available in 28 individuals who did not present to the laboratory. The patient with elevation in liver function tests had known extensive liver metastases, with improvement after PRRT.

Evaluation of ^{68}Ga-DOTATATE Imaging and Safety

Most participants, 56 (58%), were female. Midgut NET was the most common tumor type (44, 56%) (Table 1). Ten of the 97 patients did not undergo a comparative ^{111}In-pentetreotide scan and were excluded from scan comparison. Another 5 patients were excluded when ^{111}In-pentetreotide imaging was performed before resection of some or all known tumor with ^{68}Ga-DOTATATE imaging performed after surgery. Another 4 patients were excluded because the time interval between ^{68}Ga-DOTATATE and ^{111}In-pentetreotide imaging exceeded 3 y. Thus, 78 participants were included for comparison of ^{68}Ga-DOTATATE and ^{111}In-pentetreotide imaging. Mean ^{68}Ga-DOTATATE activity was 196 MBq (5.3 mCi) (95% CI, 178–215 MBq [4.8–5.8 mCi]). Median time between scans was 176 d, with an interquartile range of 105–354 d. Of the 78 participants with comparable scans, 50 had evidence of primary or metastatic disease, and 28 had no disease or stable disease.

Assessment of Test Accuracy. ^{68}Ga-DOTATATE and ^{111}In-pentetreotide scans had equivalent results in 61 of 78 (78%) patients (Fig. 1). One individual was false-positive by both scans, confirmed by biopsy, and 1 was false-negative by both methods, with tumor confirmed by other imaging. Among the 17 participants with scan disagreement, ^{111}In-pentetreotide was false-positive in 2 and ^{68}Ga-DOTATATE was false-positive in 1. The sensitivity of ^{68}Ga-DOTATATE imaging (96%; 95% CI, 86%–100%) was higher than that of ^{111}In-pentetreotide imaging by all methods (72%; 95% CI, 58%–84%) and was also higher (97%; 95% CI, 82%–100%) in the subgroup of patients with ^{111}In-pentetreotide SPECT/CT scans (83%; 95% CI, 64%–94%). ^{111}In-pentetreotide SPECT/CT was more sensitive than planar only or planar plus SPECT imaging of ^{111}In-pentetreotide. Specificity was the same for ^{68}Ga-DOTATATE and ^{111}In-pentetreotide (93%; 95% CI: 77%–99%) among all ^{111}In-pentetreotide scan types and also for the SPECT/CT subgroup. Overall accuracy for ^{68}Ga-DOTATATE (0.94; 95% CI, 0.89–1.00) was significantly higher ($P = 0.02$) than for ^{111}In-pentetreotide (0.82; 95% CI: 0.74–0.90) (Table 2). ^{68}Ga-DOTATATE and ^{111}In-pentetreotide imaging did not convey the same diagnostic result (McNemar χ^2 $P = 0.01$) in this population of mixed NET.

Assessment of ^{68}Ga-DOTATATE Interobserver Variability

Bias-corrected Fleiss κ was 0.82 (95% CI, 0.74–0.89) between the 3 reviewers in their interpretation of the 97 ^{68}Ga-DOTATATE scans. This high level of agreement was similar between various combinations of blinded versus nonblinded clinical interpreters (Supplemental Table 1), demonstrating a high level of reproducibility in ^{68}Ga-DOTATATE scan interpretations.

Assessment of Impact on Patient Care

The addition of the ^{68}Ga-DOTATATE imaging resulted in no impact on treatment plans in 50 of 78 (64%), a minor (within modality) change in 9 of 78 (12%), and a major change in treatment modality in 19 of 78 (24%) patients. Of the 19 patients with a major change due to ^{68}Ga-DOTATATE imaging, 8 had surgery cancelled or a radical change in type of surgery, and 12 patients were referred for PRRT (Fig. 2). Among 48 patients with treatment changes with ^{111}In-pentetreotide SPECT/CT scans, ^{68}Ga-DOTATATE imaging led to major changes in 11 of 78 (14%). Furthermore, time between ^{68}Ga-DOTATATE and ^{111}In-pentetreotide imaging was broken into 3 categories, 0–90 d, 91–180 d, and more than 180 d (Table 3). Changes in treatment plans were similar between the 3 time categories, with the highest proportion of scans having an impact on treatment in the 0–90 d category (44%) and least in the 91–180 d category (30%), though the differences were not significant.

^{68}Ga-DOTATATE and ^{111}In-pentetreotide scans were concurrently false-negative in 1 patient with tumor found on CT and MRI, but the 2 scans yielded useful information by demonstrating that the patient was not likely to benefit from PRRT. ^{68}Ga-DOTATATE imaging demonstrated that 12 of 78 (15%) patients were nonsurgical candidates, with strong uptake to support PRRT, of which 3 of

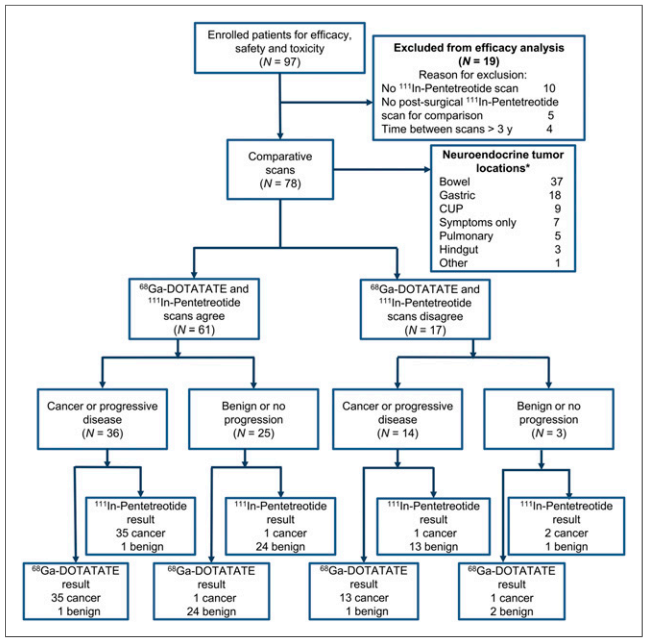

FIGURE 1. Standards for reporting diagnostic accuracy (STARD) flow diagram of ^{68}Ga-DOTATATE and ^{111}In-pentetreotide results. ^{68}Ga-DOTATATE = ^{68}Ga-DOTATATE PET/CT scan; ^{111}In-pentetreotide = ^{111}In-pentetreotide scans of all types (planar, SPECT, or SPECT/CT). *Bowel = small or large bowel; Gastric = gastric, duodenal, or pancreatic primary tumors. CUP = metastatic carcinoma with unknown primary.

TABLE 2
Contingency Tables Comparing ^{68}Ga-DOTATATE PET/CT and ^{111}In-Pentetreotide Imaging for All Patients (n = 78)

Scan type	^{111}In-pentetreotide				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
	Cancer or progression, all types	Cancer or progression, SPECT/CT	Benign, all types	Benign, SPECT/CT				
^{68}Ga-DOTATATE PET/CT								
Cancer	48	28	2	1				
Benign	2	1	26	18				
^{111}In-pentetreotide								
Cancer	36	24	2	1				
Benign	14	5	26	18				
^{68}Ga-DOTATATE PET/CT					96% (86–100)	93% (77–99)	96% (86–100)	93% (77–99)
^{111}In-pentetreotide, all types					72% (58–75)	93% (77–99)	95% (82–99)	65% (48–94)

Diagnosis based on single or multiple CT or MRI scans, surgical tissue confirmation, or combination thereof. Prevalence = 64% (95% CI, 52–75).
PPV = positive predictive value; NPV = negative predictive value.

12 (25%) were misclassified by ^{111}In-pentetreotide as not candidates for PRRT (Fig. 3).

DISCUSSION

^{68}Ga-DOTATATE PET/CT imaging has been in widespread clinical use outside the United States for nearly a decade, largely replacing ^{111}In-pentetreotide imaging where available. Space constraints in this report preclude full discussion, but an excellent systematic review and meta-analysis of ^{68}Ga-DOTATATE and similar somatostatin PET imaging analogs by Geijer and Breimer (*27*) demonstrated pooled sensitivity and specificity for these imaging agents of 0.93 (95% CI, 0.91–0.94) and 0.96 (95% CI, 0.95–0.98), respectively, with the area under the summary receiver-operating-characteristic curve of 0.976. ^{68}Ga-DOTATATE PET/CT–specific information can be found in their citations, and also in Hofman et al. (*23*) and Srirajaskanthan et al. (*28*), who provide direct comparison to ^{111}In-pentetreotide imaging. Recently Has Simsek et al. (*29*) and Lococo et al. (*30*) reported the complementary roles of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT.

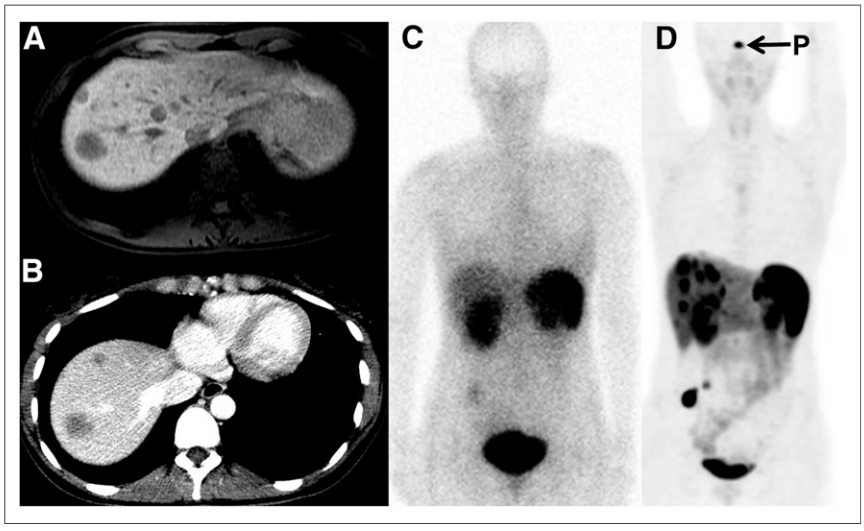

FIGURE 2. Axial gadoxetate disodium (Eovist; Bayer) MRI (A) and intravenous contrast-enhanced CT (B) images reveal some of the widespread metastatic disease in liver. Anterior planar ^{111}In-pentetreotide scan (C) and SPECT/CT (not shown) demonstrate uptake only in primary ileal tumor in abdominal right lower quadrant. On the basis of these findings, the patient would not be a candidate for PRRT treatment. ^{68}Ga-DOTATATE PET/CT (only 3-dimensional anterior maximum-intensity projection shown in D) demonstrates intense uptake in primary tumor, a locoregional node, and liver metastases, showing that patient has sufficient somatostatin receptor expression to qualify for PRRT, among other treatments. Arrow indicates normal pituitary uptake (P).

^{68}Ga-DOTATATE PET/CT is a more sensitive functional test than ^{111}In-pentetreotide imaging in our 78 patients with NETs and comparative scans, with 1 false-positive scan resulting in a biopsy. ^{68}Ga-DOTATATE PET/CT was superior to ^{111}In-pentetreotide imaging in a 48-patient subset with ^{111}In-pentetreotide SPECT/CT scans.

In 12 patients found by ^{68}Ga-DOTATATE to have sufficient somatostatin receptor expression to support PRRT, 3 were misclassified by ^{111}In-pentetreotide and would have been denied PRRT, a treatment currently under study for benefit. We found that correct clinical management could be made in all patients with imaging limited to ^{68}Ga-DOTATATE plus diagnostic CT or contrast-enhanced liver MRI, excluding the 1 false-positive examination from splenosis. No patient management decisions would have been adversely affected by excluding the ^{111}In-pentetreotide scan,

TABLE 3
Impact of ^{68}Ga-DOTATATE Scan on Clinical Care Compared with Days Between Comparison Scans

^{111}In-pentetreotide, treatment impact	Interval between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans								Interval between CT or MRI and ^{68}Ga-DOTATATE scans			
	0–30 d		0–90 d		91–180 d		>180 d					
	All types	Planar + SPECT/CT	All types	Planar + SPECT/CT	All types	Planar + SPECT/CT	All types	Planar + SPECT/CT	0–30 d	0–90 d	91–180 d	> 180 d
None	1	1	9	4	16	13	25	14	22	33	7	10
Minor	2	2	3	2	3	2	3	2	3	6	3	0
Major	0	0	4	3	4	2	11	6	5	9	4	6

All ^{111}In-pentetretotide scan types, $n = 78$, and ^{111}In-pentetretotide with SPECT/CT, $n = 48$. There was no significant impact on care by time interval between scans.

whereas 28 of 78 (36%) patients would have been adversely affected if the ^{68}Ga-DOTATATE scan had not been obtained.

The ^{111}In-pentetreotide scans were not of uniform quality, reflecting the range of protocols and equipment in the U.S. health care system. Some were performed with planar imaging only, some with planar and SPECT imaging, and some with planar and SPECT/CT. The planar with SPECT/CT imaging group provided the best comparison to ^{68}Ga-DOTATATE PET/CT. Accordingly, we performed a subanalysis comparing these 2 imaging modalities (Table 3). The results of this subanalysis showed that the accuracy of ^{111}In-pentetreotide SPECT/CT was higher than that of planar or planar with SPECT but was not as accurate as ^{68}Ga-DOTATATE PET/CT, with much of this difference driven by the number of malignant lesions missed by ^{111}In-pentetreotide, seen by ^{68}Ga-DOTATATE, especially in lymph nodes, intramedullary skeletal metastases, and distant (extraabdominal) metastases. This difference in test accuracy is also reflected in the 19 patients who had major changes in their treatment plans because of additional metastatic disease detected with ^{68}Ga-DOTATATE PET/CT.

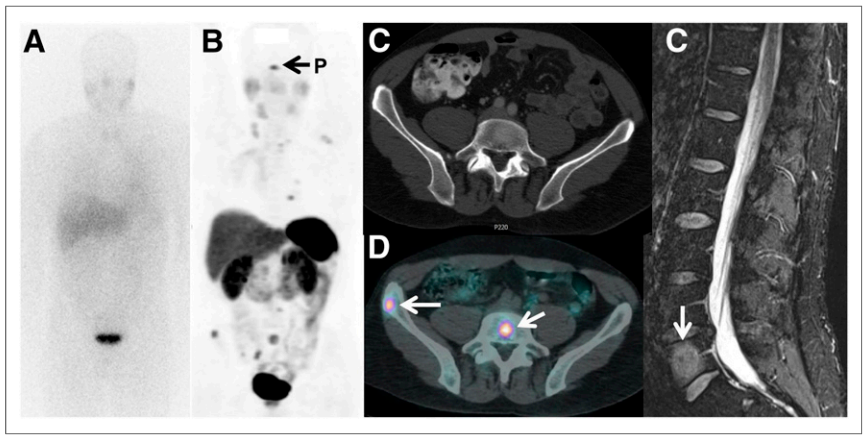

FIGURE 3. True-positive ^{68}Ga-DOTATATE PET/CT with false-negative ^{111}In-pentetreotide SPECT/CT. Anterior planar (A) image from ^{111}In-pentetreotide SPECT/CT scan was negative for residual tumor. Anterior 3-dimensional maximum-intensity-projection view (B) and fused PET/CT (D) with skeletal metastatic foci prospectively missed on contrast-enhanced CT (C), verified with MRI (selected short-τ inversion recovery image, (E)). Patient was referred for PRRT, which would have been denied based on false-negative ^{111}In-pentetreotide scan. Arrow indicates normal pituitary uptake (P).

One intense focus of ^{68}Ga-DOTATATE was in the head of the pancreas, a known area of frequent intense, focal uptake of ^{68}Ga-DOTATATE that can also be seen with ^{111}In-pentetreotide (*23*). Because we knew of this frequent finding, no adverse impact on care resulted, with absence of tumor confirmed by CT. The single known false-positive result was due to splenosis and inflammation, confirmed at surgery, though surgery was already planned.

Interobserver reliability between the nonblinded, fully informed ^{68}Ga-DOTATATE interpreter and the 2, independent, blinded interpreters demonstrated the high degree of reproducibility of interpretation in this trial by experienced interpreters on a per-patient basis. The κ statistic of 0.82 represents superior to near-perfect agreement between the 3 interpreters.

This study has some limitations. As it is neither feasible nor ethical to obtain histologic confirmation of all sites of apparent tumor, the impact on care for ^{68}Ga-DOTATATE versus ^{111}In-pentetreotide imaging was analyzed on a per-patient, not a per-lesion, basis. The ^{68}Ga-DOTATATE scan was added to the full clinical assessment of the patient performed before the ^{68}Ga-DOTATATE scan, using all prior imaging and clinical information, to determine whether the addition of the ^{68}Ga-DOTATATE scan changed the treatment plan, similar to other reports (*23,28,31*). The sensitivity and specificity of both ^{111}In-pentetreotide and ^{68}Ga-DOTATATE in our trial may not reflect the true accuracy of either test because of an imperfect gold standard bias arising from using per-patient rather than per-lesion analysis. To minimize the bias from this imperfect gold standard, we focused on comparing clinical management impact rather than the possibly imperfect final diagnosis (*32*).

Importantly, this is the first report, to our knowledge, with quantitative toxicity data for ^{68}Ga-DOTATATE, with prior reporting typically limited to general observation due to differences in regulatory requirements for investigators outside the United States for drug mass microdose quantities (*33*). Although acute toxicity data were available in all 97 patients, our study is limited by some random post-scan organ function or hematologic toxicity

data missing in 28 patients. Many patients traveled great distances to us, limiting our access to follow-up laboratory tests, especially in a timely manner. However, in the data we have for all 97 patients, we observed no toxicity that was symptomatic or otherwise requiring treatment.

Another limitation of our study is that not all patients had identical imaging protocols for CT, MRI, or ^{111}In-pentetreotide scanning. Not all had both CT and MRI examinations, and the quality of the outside studies reflected the range in image quality throughout the United States. Also, because not all of our patients had health care insurance, not all could afford the requested follow-up laboratory tests.

CONCLUSION

^{68}Ga-DOTATATE PET/CT changed management in 37% of patients. ^{111}In-pentetreotide did not add value compared with ^{68}Ga-DOTATATE in any patient. When diagnostic imaging is limited to whole-body ^{68}Ga-DOTATATE plus diagnostic CT or liver MRI, correct staging and treatment decisions would have been reached in all patients. Our results clearly demonstrate that ^{68}Ga-DOTATATE PET/CT is equivalent or superior to ^{111}In-pentetreotide imaging for the diagnosis and staging of lung and gastroenteropancreatic NETs. Given the superior performance for tumor detection (McNemar χ^2, $P = 0.01$), lower radiation dosimetry (*25*), and 2-h completion time compared with 2 d for ^{111}In-pentetreotide imaging, our results conclusively demonstrate that ^{68}Ga-DOTATATE PET/CT imaging is safe and should replace ^{111}In-pentetreotide imaging, where available.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. Support for this study was provided by the U.S. Department of Veterans Affairs Merit Review, I01BX007080; the Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network; Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS/NIH); and local institutional and philanthropic support. ^{68}Ga-DOTATATE is not U.S. Food and Drug Administration–approved for human use outside a properly conducted clinical trial. No other potential conflict of interest relevant to this article was reported.

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