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

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Running title: Toxicity/Efficacy - $^{68}$Ga-DOTATATE

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ABSTRACT

Rationale
Our purpose was to evaluate safety and efficacy of $^{68}$Ga-DOTATATE PET/CT compared to $^{111}$In-Pentetreotide imaging for diagnosis, staging and re-staging of pulmonary and gastroenteropancreatic (GEP) neuroendocrine tumors (NETs).

Methods
$^{68}$Ga-DOTATATE PET/CT and $^{111}$In-Pentetreotide scans were performed in 78 of 97 consecutively enrolled patients with known or suspected pulmonary or GEP NETs. 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. Inter-observer reproducibility of $^{68}$Ga-DOTATATE PET/CT scan interpretation was measured between blinded and non-blinded readers.

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 and/or liver MRI changed care in 28 of 78 (36%) patients. Inter-observer agreement between blinded and non-blinded readers was very high. No participant had a trial-related event requiring treatment. Mild, transient events were tachycardia in one, alanine transaminase elevation in one and hyperglycemia in two 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.

Conclusions
$^{68}$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 to $^{111}$In-Pentetreotide. $^{68}$Ga-DOTATATE imaging should be used instead of $^{111}$In-Pentetreotide imaging where available.
INTRODUCTION

Neuroendocrine tumors (NETs) are usually slow-growing malignancies, mostly of the respiratory and digestive tracts, that cause significant morbidity and mortality (1). While generally considered rare due to 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). NET can be difficult to diagnose because of protean clinical presentations. Common chronic symptoms include cough or diarrhea, while others are clinically silent. The average time from symptom onset to diagnosis can be up to 9 years (3). Despite its reputation as a relatively “benign” disease, NETs are highly metastatic with most broncho-pulmonary 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 analogues, biologics, molecularly target 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 computed tomography (CT) and magnetic resonance imaging (MRI), provide critical information, but are limited in their fields of view and are 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 analogues conjugated to $^{111}$In allows whole body imaging with planar and/or single photon emission tomography (SPECT), or SPECT/CT (17) the gold-standard for NET imaging for over two decades (18, 19). However, positron emission tomography with CT (PET/CT), developed in this interim, has higher resolution than SPECT. In
oncology, FDG PET/CT is the imaging reference for most malignancies. Outside the United States, PET/CT with somatostatin analogues 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-labeled 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-D-Phe$^1$,Tyr$^3$-octreotate ($^{68}$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 to $^{111}$In-Pentetreotide imaging.

**PATIENTS AND METHODS**

**Patient Population**

This study is investigator-initiated with extramural (VA Merit Review I01BX007080 and Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network) and local philanthropic and institutional support, and is a registered US clinical trial (NCT01396382). Neuroendocrine cancer is a designated orphan disease, and $^{68}$Ga-DOTATATE is a designated orphan drug, by the US FDA. In this study of 98 $^{68}$Ga-DOTATATE PET/CT scans performed on 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 in all subjects, with local IRB approval and oversight (Vanderbilt University Medical Center IRB#110588), and US FDA investigational new drug approval (IND 111972). The initial two patients were scanned with individual compassionate use INDs 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 to $^{111}$In-Pentetreotide scan 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 years. Safety and toxicity were assessed with pre-injection and post-imaging 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 dosimetry is less than comparable $^{111}$In-Pentetreotide or $^{18}$F-FDG PET/CT scans(25).

No special dietary or activity restrictions were needed since $^{68}$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 micrograms or less. Long-acting somatostatin analog medications are useful for symptomatic control and for anti-proliferative therapy of NETs. Thus, patients on long-acting somatostatin analog medications ($N=51$) did not stop these medications prior to undergoing $^{68}$Ga-DOTATATE PET/CT.

Imaging was performed with an 8-slice Discovery STE PET/CT full-ring integrated scanner (GE Healthcare, Waukesha, WI), beginning 65 min (range 55 – 93) after injection. Immediately after emptying their urinary bladders, a low-dose CT was performed from skull vertex to mid-thighs for attenuation correction and anatomic localization. Emission imaging (3D mode, 4 minutes 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 hours. CT reconstruction was with filtered back-projection, with emission image reconstruction via OSEM 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 \textsuperscript{111}In-Pentetreotide imaging from outside facilities with them in digital format. All outside images and original reports were loaded onto the Vanderbilt University Medical Center’s Picture Archive and Cataloging System linked to the Vanderbilt electronic healthcare records of each patient.

Because it was neither feasible nor ethical to obtain histological confirmation of all sites of apparent metastatic tumor, diagnosis and impact on care for \textsuperscript{68}Ga-DOTATATE vs. \textsuperscript{111}In-Pentetreotide imaging was analyzed on a “per-patient,” not a per-lesion, basis. Diagnosis and scoring for the extent of disease was determined using a combination of the preponderance of evidence from conventional imaging and pathological specimens prior to \textsuperscript{68}Ga-DOTATATE imaging, and then adding \textsuperscript{68}Ga-DOTATATE scan results to the full clinical assessment of the patient using all available prior imaging and clinical information, to determine if the addition of the \textsuperscript{68}Ga-DOTATATE scan changed the treatment plan. Evidence for tumor was scored based on original reports from conventional imaging, as well as abnormal, especially focal, areas of uptake on \textsuperscript{111}In-Pentetreotide or \textsuperscript{68}Ga-DOTATATE imaging. Scan results from the three independent \textsuperscript{68}Ga-DOTATATE readers were entered into an spreadsheet, along with the original reports on conventional and \textsuperscript{111}In-Pentetreotide imaging, and then analyzed for presence/absence of tumor, tumor improved, stable or progressive compared to earlier scans, and whether, and how, the results of the \textsuperscript{68}Ga-DOTATATE PET/CT scan changed patient management compared to either \textsuperscript{111}In-Pentetreotide alone and/or in combination with CT and/or MRI. Changes in management decision were determined and recorded via consensus of a weekly multidisciplinary neuroendocrine tumor 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’s chi-square test and by comparison of receiver operator curves for differences of diagnostic test accuracy.

Original clinical reports of $^{111}$In-Pentetreotide, CT and MRI exams were used for analysis of these exams even if, in retrospect, additional sites of tumor were seen after comparison to $^{68}$Ga-DOTATATE images. $^{68}$Ga-DOTATATE imaging was interpreted via two 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 inter-observer reproducibility, two board-certified nuclear medicine physicians independently interpreted the $^{68}$Ga-DOTATATE scans, blinded to all information, including other imaging, beyond knowing the patient met enrollment criteria. The two blinded interpretations were recorded on a regional basis (solid organ, regional nodal, regional extranodal abdominal and pelvic involvement, extra-abdominal/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 kappa and confidence interval estimated using bootstrap method. The three physicians involved with $^{68}$Ga-DOTATATE scan interpretation each have 30+ years’ experience in medical imaging and 10+ years’ experience in PET/CT interpretation.

Separately, a board-certified oncological surgeon assessed the impact on care by comparing the intended treatment prior to and after the $^{68}$Ga-DOTATATE scan, on a per-patient basis. 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 due to evidence of greater extent of disease on $^{68}$Ga-DOTATATE scan, are examples of major, intramodality treatment changes.

Data Analysis

Toxicity data were compiled and individual patient test results pre- and post-scan were compared. Blood laboratory test values include some fasting and non-fasting results as fasting status was not recorded. The cohorts’ pre- and post-scan test mean, median, standard errors and inter-quartile ranges are reported in Supplemental File Appendix 1. Statistically significant differences in test values were assessed by paired t-test and the non-parametric Wilcoxon rank-sum test. All tests are two-sided and performed using Stata, College Station, TX. Harm was measured by National Cancer Institute, Common Toxicity Criteria Version 1 (http://www.accessdata.fda.gov/scripts/cder/onctools/toxcrit1.cfm) with blood laboratory test values within the normal range having harm level 0. All participants were included for toxicity measurement.

RESULTS

Toxicity/Safety

No serious adverse events occurred among the 97 participants. Additional co-morbidities influencing abnormal baseline, pre-injection ECGs included: various conduction defects, one patient with ECG evidence of a prior anteroseptal infarction with a left anterior fascicular block, two patients with T-wave inversions, two with nonspecific ST-T wave changes, two with first degree AV block, two with p-wave abnormalities, one with a ventricular paced rhythm and one
with a prior cardiac transplant. No serious arrhythmias, changes in Q-T interval, or other significant changes from baseline, were observed.

Minor adverse events occurred in three 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 post-scan oxygen saturation on room air (pre-injection 98%, post scan 90%), spontaneously resolving. One patient with a baseline heart rate of 87 had post-scan tachycardia of 112, asymptomatic, spontaneously returning to <100 beats per minute within an hour. Other patients had minor and transient changes in laboratory tests, all asymptomatic. Elevated glucose was observed in two patients (both on long-acting somatostatin analog medication, known to cause glucose intolerance in up to 25% of patients; one of these two patients is a diabetic). Post-scan fasting glucose plasma levels could not be consistently obtained after the participants returned home, so these two 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**

The majority of participants, 56 (58%), were female. Mid-gut NET was the most common tumor type (44, 56%) (Table 1). Ten of the 97 patients did not have a comparative $^{111}$In-Pentetreotide scan and were excluded from scan comparison. Another 5 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 were excluded because the time interval between $^{68}$Ga-DOTATATE and $^{111}$In-Pentetreotide imaging exceeded 3 years. Thus, 78 participants were included for comparison of $^{68}$Ga-DOTATATE and $^{111}$In-Pentetreotide imaging. Mean $^{68}$Ga-DOTATATE activity was 196 MBq (5.3mCi) (95%CI: 178, 215 MBq; 4.8, 5.8 mCi). Median time between scans was 176 days with an inter-quartile range of 105 to 354 days. 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 61/78 (78%) patients (Fig. 1). One individual was false positive by both scans, confirmed by biopsy, and one 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 two and $^{68}$Ga-DOTATATE was false positive in one. The sensitivity of $^{68}$Ga-DOTATATE imaging (96%; 95%CI: 86%, 100%) was higher than $^{111}$In-Pentetreotide imaging by all methods, (72%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’s chi-square p=0.01) in this population of mixed NET.

**Assessment of $^{68}$Ga-DOTATATE Inter-observer Variability**

Bias corrected Fleiss Kappa was 0.82 (95%CI: 0.74, 0.89) between the three reviewers in their reading of the 97 $^{68}$Ga-DOTATATE scans. This high level of agreement was similar between various combinations of blinded vs. non-blinded clinical readers (Supplemental Table 1) demonstrating a high level of reproducibility in $^{68}$Ga-DOTATATE scan interpretations.

**Assessment of Impact on Patient Care:**

12
The addition of the $^{68}$Ga-DOTATATE imaging resulted in no impact on treatment plans in 50/78 (64%), a minor (within modality) change in 9/78 (12%), and a major change in treatment modality in 19/78 (24%) of patients. Of the 19 patients with a major change due to $^{68}$Ga-DOTATATE imaging, eight 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 11/78 (14%). Furthermore, time between $^{68}$Ga-DOTATATE and $^{111}$In-Pentetreotide imaging was broken into three categories, 0 to 90 days, 91 to 180 days and more than 180 days (Table 3). Changes in treatment plans were similar between the three time categories with the highest proportion of scans having an impact on treatment in the 0 to 90 days category (44%) and least in the 91 to 180 days (30%), though the differences were not significant.

$^{68}$Ga-DOTATATE and $^{111}$In-Pentetreotide scans were concurrently false negative in one patient with tumor found on CT and MRI, but the two scans yielded useful information by demonstrating that the patient was not likely to benefit from PRRT. $^{68}$Ga-DOTATATE imaging demonstrated that 12/78 (15%) patients were nonsurgical candidates, with strong uptake to support PRRT, of which 3/12 (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 US 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 (with 95% confidence intervals) for these imaging agents of 0.93 (0.91 to 0.94) and 0.96 (0.95 to 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.

$^{68}$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 one 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 SSTR 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 and/or contrast-enhanced liver MRI, excluding the one false positive exam from splenosis. No patient management decisions would have been adversely impacted by excluding the $^{111}$In-Pentetreotide scan, whereas 28/78 (36%) patients would have been adversely impacted if the $^{68}$Ga-DOTATATE scan had not been performed.
The $^{111}$In-Pentetreotide scans were not of uniform quality, reflecting the range of protocols and equipment in the US healthcare 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 sub-analysis comparing these two imaging modalities (Table 3). The results of this sub-analysis showed that the accuracy of $^{111}$In-Pentetreotide scan 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 (extra-abdominal) metastases. This difference in test accuracy is also reflected in the 19 patients who had major changes in their treatment plans due to additional metastatic disease detected with $^{68}$Ga-DOTATATE PET/CT.

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.

Inter-observer reliability between the non-blinded, fully informed $^{68}$Ga-DOTATATE reader and the two, independent, blinded readers, demonstrated the high degree of reproducibility of interpretation in this trial by experienced readers on a per-patient basis. The kappa statistic of 0.82 represents superior to near perfect agreement between the three interpreters.

**Limitations**
As it is neither feasible nor ethical to obtain histological confirmation of all sites of apparent tumor, the impact on care for $^{68}$Ga-DOTATATE vs. $^{111}$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 prior to the $^{68}$Ga-DOTATATE scan, using all prior imaging and clinical information, to determine if 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 due to 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 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 “micro-dose” quantities (33). Although acute toxicity data was 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 in 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 healthcare insurance, not all could afford the requested follow-up laboratory tests.

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

Supplemental Appendix 1 - Toxicity

Supplemental Table 1 - Inter-observer variability
REFERENCES


Figure 1: STARD flow diagram of $^{68}$Ga-DOTATATE and $^{111}$In-Pentetreotide results

Note: STARD = standards for reporting diagnostic accuracy; $^{68}$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
Fig. 2. Axial gadoxetate disodium (Eovist™) MRI (A) and IV contrast enhanced CT (B) images reveal some of the widespread metastatic disease in the liver. Anterior planar $^{111}$In-Pentetrotide scan (C) and SPECT/CT (not shown) demonstrate uptake only in the primary ileal tumor in the abdominal right lower quadrant. Based on these findings, the patient would not be a candidate for PRRT treatment. $^{68}$Ga-DOTATATE PET/CT (only 3D anterior maximum intensity projection shown, (D)) demonstrates intense uptake in the primary tumor, a locoregional node and the liver metastases, demonstrating that the patient has sufficient somatostatin receptor expression to qualify for PRRT, among other treatments. The arrow indicates normal pituitary uptake (P).
Fig. 3. True positive $^{68}$Ga-DOTATATE PET/CT with false-negative $^{111}$In-Pentetreotide SPECT/CT. Anterior planar (A) image from an $^{111}$In-Pentetreotide SPECT/CT scan was negative for residual tumor. Anterior 3D 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-tau inversion recovery image, (E). The patient was referred for PRRT, which would have been denied based on the false negative $^{111}$In-Pentetreotide scan. The arrow indicates normal pituitary uptake (P).
Table 1 Participant Demographics of Patients with Comparable Scans

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<thead>
<tr>
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<th>All Patients Enrolled</th>
<th>¹¹¹In-Pentetreotide and ⁶⁸Ga-DOTATATE scans</th>
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<td></td>
<td>N = 97</td>
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<td>Gender Female (%)</td>
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<td>Mean Age (SD)</td>
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<td>Neuroendocrine tumor type (%)</td>
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<tr>
<td>Planar + SPECT</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Planar + SPECT/CT</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Outside scan, type not specified</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Days between ¹¹¹In-Pentetreotide and ⁶⁸DOTATATE scans:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 90 days:</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>91 – 180 days:</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>&gt; 180 days:</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>Ki-67 Category:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Intermediate</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>High</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Missing</td>
<td>30</td>
<td>26</td>
</tr>
</tbody>
</table>
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 | | | |
|---|---|---|---|
| | Cancer or progression | Cancer or progression | Benign | Benign |
| $^{68}$Ga-DOTATATE PET/CT | All Types SPECT/CT | All Types SPECT/CT | | |
| Cancer | 48 | 28 | 2 | 1 |
| Benign | 2 | 1 | 26 | 18 |
| | Cancer or progression | Cancer or progression | Benign | Benign |
| $^{111}$In-Pentetreotide | All Types SPECT/CT | All Types SPECT/CT | | |
| Cancer | 36 | 24 | 2 | 1 |
| Benign | 14 | 5 | 26 | 18 |
| | SENS 95% CI | SPEC 95% CI | PPV 95% CI | NPV 95% CI |
| $^{68}$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 and/or MRI scans, surgical tissue confirmation, or a combination thereof.

95%CI = 95% confidence interval

Prevalence = 64%, 95%CI 52, 75
Table 3 Impact of $^{68}$Ga-DOTATATE scan on clinical care compared to days between comparison scans.

<table>
<thead>
<tr>
<th>Days:</th>
<th>Interval between $^{111}$In-Pentetretotide and $^{68}$Ga-DOTATATE scans</th>
<th>0 – 30 days</th>
<th>0 – 90 days</th>
<th>91 – 180 days</th>
<th>&gt; 180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{111}$In-Pentetretotide scan type</td>
<td>All Types</td>
<td>Planar + SPECT/CT</td>
<td>All Types</td>
<td>Planar + SPECT/CT</td>
<td>All Types</td>
</tr>
<tr>
<td>Treatment Impact</td>
<td>None</td>
<td>Minor</td>
<td>Major</td>
<td>None</td>
<td>Minor</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Interval between CT and/or MRI and $^{68}$Ga-DOTATATE scans

<table>
<thead>
<tr>
<th>Days:</th>
<th>Interval between CT and/or MRI and $^{68}$Ga-DOTATATE scans</th>
<th>0 – 30 days</th>
<th>0 – 90 days</th>
<th>91 – 180 days</th>
<th>&gt; 180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Impact</td>
<td>None</td>
<td>Minor</td>
<td>Major</td>
<td>None</td>
<td>Minor</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>33</td>
<td>7</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>9</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

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

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