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^{64}Cu-DOTATATE PET/CT for Imaging Patients with Known or Suspected Somatostatin Receptor-Positive Neuroendocrine Tumors: Results of the First US Prospective, Reader-Blinded Clinical Trial

Ebrahim S. Delpassand[1,2], David Ranganathan[2], Nilesh Wagh[2], Afshin Shafie[1], Ayman Gaber[1], Ali Abbasi[2], Andreas Kjaer[3], Izabela Tworowska[2], and Rodolfo Núñez[1]

[1]Excel Diagnostics and Nuclear Oncology Center, Houston, TX (USA); [2]RadioMedix, Inc. Houston, TX (USA); [3]Department of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Rigshospitalet and University of Copenhagen, Denmark

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Corresponding author

Rodolfo Núñez, M.D.

Excel Diagnostics and Nuclear Oncology Center

9701 Richmond Ave, Suite 122

Houston, TX 77042

Phone: 713-781-6200

FAX: 713-781-6206

rnunez@exceldiagnostics.com

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ABSTRACT (word count: 349 [limit 350 words])

Studies demonstrate that the investigational ^{64}Cu-DOTATATE radiopharmaceutical may provide diagnostic and logistical benefits over available imaging agents for patients with somatostatin receptor (SSTR)-positive neuroendocrine tumors (NETs). Accordingly, we aimed to prospectively determine the lowest dose of ^{64}Cu-DOTATATE that facilitates diagnostic quality scans and evaluated the diagnostic performance and safety in a phase III study of patients with SSTR-expressing NETs. **Methods:** A dose-ranging study was conducted in 12 patients divided into 3 dose groups (111 MBq [3.0 mCi], 148 MBq [4.0 mCi], and 185 MBq [5.0 mCi] ± 10%) to determine the lowest dose of ^{64}Cu-DOTATATE that produced diagnostic quality PET/CT images. Using the ^{64}Cu-DOTATATE dose identified in the dose-ranging study, 3 independent nuclear medicine physicians who were blinded to all clinical information read PET/CT scans from 21 healthy volunteers and 42 NET-positive patients to determine those with "Disease" and "No Disease," as well as "Localized" versus "Metastatic" status. Blinded-reader evaluations were compared to a patient-specific standard of truth (SOT), which was established by an independent oncologist who used all previously available pathology, clinical, and conventional imaging data. Diagnostic performance calculated for ^{64}Cu-DOTATATE included sensitivity, specificity, negative predictive value, positive predictive value, and accuracy. Inter- and intra-reader reliability, as well as ability to differentiate between localized and metastatic disease, was also determined. Adverse events (AEs) were recorded from ^{64}Cu-DOTATATE injection through 48 hours post-injection. **Results:** The dose-ranging study identified 148 MBq (4.0 mCi) as the optimal dose to obtain diagnostic quality PET/CT images. Following database lock, diagnostic performance from an initial majority read of the 3 independent readers showed a significant 90.9% sensitivity ($P = 0.0042$) and 96.6% specificity ($P < 0.0001$) for detecting NETs, which

translated to a 100.0% sensitivity and 96.8% specificity after correcting for an initial SOT misread. Excellent inter- and intra-reader reliability, as well as ability to distinguish between localized and metastatic disease, was also noted. No AEs were related to ^{64}Cu-DOTATATE, and no serious AEs were observed. **Conclusion:** ^{64}Cu-DOTATATE PET/CT is a safe imaging technique that provides high-quality and accurate images at a dose of 148 MBq (4.0 mCi) for the detection of somatostatin-expressing NETs.

Key Words: ^{64}Cu-DOTATATE, clinical phase III trial, prospective study, neuroendocrine tumors, PET/CT in oncology.

INTRODUCTION

The incidence of neuroendocrine tumors (NETs) has increased 6.4-fold in the United States since 1973, with the greatest increase being observed in localized, well-differentiated Grade 1 NETs (*1*). The increase in NET diagnoses is likely due in part to advances in diagnostic imaging (*1*). The use of somatostatin receptor (SSTR) scintigraphy with ^{111}In-DTPA-octreotide (Octreoscan ™) in the mid 1990s significantly improved the accuracy with which patients with NETs were identified, staged, and monitored. Octreotide is a somatostatin analogue that binds specifically to SSTRs type 2 and 5 and allows the molecular imaging and characterization of NETs (*2,3*). After determining SSTR positivity with ^{111}In-DTPA-octreotide single photon emission computed tomography (SPECT), peptide receptor radionuclide therapy (PRRT) could then be instituted using therapeutic radionuclides (eg, ^{177}Lu, ^{90}Y) labeled with the same peptide for personalized treatment (*4*). However, ^{111}In-DTPA-octreotide was constrained by limitations in image quality and spatial resolution, as well as prolonged imaging protocols (*5,6*).

In 2016, the US Food and Drug Administration approved the radiopharmaceutical ^{68}Ga-DOTATATE to be used with positron emission tomography (PET), an imaging modality with higher resolution compared with SPECT (*3*). Additionally, the higher affinity of DOTATATE compared with DTPA-octreotide to SSTR type 2 further increased the sensitivity, specificity, and accuracy of detecting SSTR-expressing NETs (*2,6*). Despite the advantages over ^{111}In-DTPA-octreotide, ^{68}Ga-DOTATATE has inherent limitations. In particular, a short 1.1-h half-life requires that it be locally produced via a generator and used proximally, limiting availability of ^{68}Ga-DOTATATE to large medical centers (*3*). The tight scanning window, moreover, complicates the precise and close coordination that is required between radiochemistry and patient scheduling personnel (*7*).

^{64}Cu-DOTATATE has been studied as a potential PET radiotracer for SSTR-based imaging. ^{64}Cu-DOTATATE is an investigational somatostatin analogue PET radiotracer that has demonstrated lower radiation dose and higher lesion detection rates compared with ^{111}In-DTPA-octreotide, as well as a superior lesion detection rate compared with ^{68}Ga-DOTATOC, in patients with NETs (*7,8*). The lower positron energy (0.65 vs 1.90 MeV), which translates to lower positron range (0.56 vs 3.5 mm), is thought to explain the anticipated improved spatial resolution and diagnostic performance of ^{64}Cu-DOTATATE over, for example, ^{68}Ga-DOTATOC (*9-11*). Additionally, the longer physical half-life (12.7 vs 1.1 h) may increase the shelf-life of ^{64}Cu-DOTATATE, eliminate reliance on a generator, and provide a more-flexible scanning window, making ^{64}Cu-DOTATATE attractive for routine clinical imaging (*2,7*).

The primary objective of this first US phase III, prospective, reader-blinded, controlled pivotal trial was to assess the sensitivity and specificity of ^{64}Cu-DOTATATE PET/computed tomography (CT) imaging for detecting NETs in subjects with or without disease against a standard of truth (SOT) for each subject. However, unlike most diagnostic performance studies, the phase III study was preceded by an independent dose-ranging study to determine the optimal dose for obtaining diagnostic-quality PET/CT images. Secondary objectives were to compare the performance of ^{64}Cu-DOTATATE using a reader-majority rule determination or individual reader determinations versus the SOT, evaluate the performance of ^{64}Cu-DOTATATE in ascertaining whether subjects had metastatic or local disease compared to the SOT, and assess inter- and intra-reader agreement. Consistent with other well-controlled diagnostic performance studies, safety was also evaluated.

MATERIALS AND METHODS

Dose-Ranging Study Design

Twelve patients with NETs were recruited into three ^{64}Cu-DOTATATE dose groups (111 MBq [3.0 mCi], 148 MBq [4.0 mCi], and 185 MBq [5.0 mCi] ± 10%) with 4 patients per group. Patient demographics and characteristics are shown in Table 1. PET/CT images were acquired at 60 ± 15 minutes after injection and with 5-minute acquisition times per bed position. Image quality was evaluated by 3 experienced readers blinded to dose information. Image quality was assessed using the following scoring system: 0 = inadequate (grainy images with poor delineation of lesions); 1 = questionable (clear images, but lesion delineation is suboptimal and small lesions [1 cm]) are hard to assess; 2 = acceptable (clear images, large and small lesion delineation is possible). Cohort scores were calculated by adding the average image subject scores in each dosing group. Consistent with the as low as reasonably achievable (ALARA) principle, the lowest dose level with a cohort score ≥7 was deemed the lowest ^{64}Cu-DOTATATE dose that provides diagnostic-quality PET/CT images. The study was approved by the Biomedical Research Alliance of New York Institutional Review Board (BRANY IRB), and all subjects gave written informed consent.

Phase III Study Design

The pivotal phase III study (NCT03673943) was an open-label, single-dose, single-arm, single-center, prospective design that evaluated the sensitivity and specificity of ^{64}Cu-DOTATATE PET/CT imaging in patients with known or suspected NETs against an independent reader's SOT for each subject; readers were blinded to the SOT. Patient demographics and characteristics are shown in Table 1. To obtain ≥90% chance of showing

>0.70 sensitivity and >0.60 specificity, 63 subjects were required. Following a pre-established 2:1 (NET-positive/NET-negative) ratio, 42 SOT-positive patients and 21 SOT-negative healthy volunteers were recruited under a US Food and Drug Administration–approved Investigational New Drug application. Of note, the 4 patients at the optimal ^{64}Cu-DOTATATE dose (148 MBq [4.0 mCi]) in the dose-ranging study were eligible and subsequently enrolled in the phase III study. NET positivity by the SOT was determined using magnetic resonance imaging, CT, ^{18}Fluorodeoxyglucose PET/CT, bone scintigraphy, ^{111}In-DTPA-octreotide scans, or ^{68}Ga-DOTATATE PET/CT. This prospective study was performed in accordance with the Helsinki Declaration and followed the International Conference on Harmonisation Good Clinical Practice guidelines. The study was also approved by the BRANY IRB, and all subjects gave written informed consent.

Synthesis and Radiolabeling of ^{64}Cu-DOTATATE

$^{64}CuCl_2$ was produced at the cyclotron facility at Washington University in St Louis, Missouri, USA, and DOTATATE peptide was manufactured by ABX GmbH in Radeburg, Germany. ^{64}Cu-DOTATATE drug was prepared by RadioMedix, Inc., in Houston, Texas, USA, according to Current Good Manufacturing Practice guidelines. Briefly, $^{64}CuCl_2$ (5550–9250 MBq) was added to sodium acetate buffer containing DOTATATE (0.4 mg) and gentisic acid (4.0 mg). The reaction mixture was incubated for 10 minutes at 95ºC then passed through a Sep-Pak C18. The cartridge-retained product was eluted with 1 mL of ethanol into a vial containing sodium ascorbate solution (50 mg/mL). The contents of the vial were filtered through a 0.22 μm filter. The final ^{64}Cu-DOTATATE drug underwent standard radiopharmaceutical quality control.

The radiochemical purity of ^{64}Cu-DOTATATE was >95% (high-performance liquid chromatography) and the average specific activity was 29.6 MBq/μg.

Image Acquisition

All subjects had a PET/CT scan performed on a SIEMENS Biograph Horizon 16-slice scanner (SIEMENS Healthineers, Malvern, Pennsylvania, USA). PET/CT scans were undertaken on average 63 minutes (median 60 mins; range: 39–97 mins) after a single intravenous dose of 148 MBq ± 10% (range: 132–163 MBq) ^{64}Cu-DOTATATE. PET scans (from vertex of the skull to mid-thigh) were obtained in 3-dimensional mode, with an acquisition time of 5 minutes per bed position over an approximately 30-minute total scan time. A non–contrast-enhanced CT scan was performed using the CT exposure factors of 140 kVp and 80 mA in 0.5 s. PET/CT images were reconstructed using CT for attenuation correction and ordered-subsets expectation maximization with 2 iterations and 24 subsets.

Image Analysis and Data Interpretation

PET/CT images acquired at the clinical site were transferred to an independent medical imaging contract research organization that blinded all clinical, imaging, and laboratory information. Thereafter, the contract research organization randomized the images to 3 experienced, independent, board-certified nuclear medicine physicians who had been trained previously by the contract research organization to detect abnormal images associated with SSTRs. Readers 1, 2, and 3 had 37, 5, and 8 years of experience in nuclear medicine, respectively, and all had read hundreds of ^{68}Ga-based SSTR PET/CT scans. Upon assessment, each physician reader categorized subjects as “Disease” or “No Disease” based only on ^{64}Cu-

DOTATATE tumor uptake. Subjects categorized as “Disease” were further sub-categorized as “Localized” or “Metastatic” as appropriate. Ten percent of the images (7 cases) were randomly selected for assessment of inter-reader variability by reintroducing the images for a second blinded read to the independent readers not earlier than 4 weeks after the primary read.

In parallel, an independent oncologist established the SOT for each subject using available scan reports from composite conventional imaging modalities and pathology studies; ^{64}Cu-DOTATATE scans were not used to establish the SOT. The SOT oncologist used the collective information to categorize each patient as “Disease” or “No Disease,” and “Localized” or “Metastatic” as appropriate.

Safety Assessments

Safety was primarily assessed through investigator-assessed treatment emergent adverse events. An adverse event was considered treatment-emergent if the start date and time was on or after the start date and time of ^{64}Cu-DOTATATE injection. Adverse events observed by the investigator or obtained during nonleading telephone interviews 24 and 48 hours postinjection were recorded using the MedDRA version 19.1 coding system from the International Council for Harmonisation. In addition, observed or patient-reported immediate adverse events were assessed within 1 hour before and 2 hours after ^{64}Cu-DOTATATE administration. Severity of adverse events was assessed independently by investigators and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, in which Grades 1, 2, 3, 4, and 5 describe adverse events as mild, moderate, severe or medically significant but not life-threatening, life-threatening, and death related to adverse event, respectively.

Vital signs were recorded within 30 minutes before and up to 1 hour after administration of ^{64}Cu-DOTATATE. Blood samples for clinical laboratory tests and hematology were collected within 30 minutes before and within 2 hours following ^{64}Cu-DOTATATE administration. All subjects also underwent continuous electrocardiogram recording at least 15 minutes prior to ^{64}Cu-DOTATATE administration with continuation for at least 30 minutes after administration. In addition, a 12-lead static electrocardiogram was performed within 60 minutes before and following ^{64}Cu-DOTATATE administration. All electrocardiogram data were collected, analyzed, and reviewed by an independent physician to determine normal versus abnormal, and whether clinically significant.

For 8 subjects of child-bearing potential, a urine pregnancy test was performed prior to imaging to rule out pregnancy.

Statistical Analysis

Confidence limits for all binomial parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using Wilson's score method with continuity correction (the score method). Each hypothesis test was conducted at the one-sided $\alpha = 0.025$ level of significance. Point estimates of sensitivity and specificity were calculated along with two-sided 95% confidence intervals using the score method. Sensitivity and specificity were calculated on a by–individual reader basis. In addition, a majority-read statistical analysis also was performed, taking into account the most favored category of reading for each subject from the 3 readers, as it was a consensus reading. Success upon the primary endpoints could be declared if 2 of the 3 independent readers achieved a sensitivity and a specificity exceeding pre-established thresholds.

Analysis of NPV, PPV, and accuracy was computed using the majority read (ie, majority ^{64}Cu-DOTATATE diagnosis from the 3 readers), as well as by-reader reports. Point estimates of the majority-read and by-reader NPV, PPV, and accuracy were calculated along with 95% confidence intervals using the score method. Sensitivity and specificity were determined relative to the SOT. The statistical analysis plan included a testable hypothesis for the coprimary endpoints (ie, sensitivity and specificity). Thus, P values were calculated for sensitivity and specificity, and not PPV, NPV, and accuracy. *P* values < 0.05 were considered statistically significant.

For the inter- and intra-reader agreement analysis of each reader pair (Readers 1 and 2, Readers 1 and 3, and Readers 2 and 3), a Cohen's kappa along with a 95% confidence interval on Cohen's kappa was computed. A 95% confidence interval for kappa was also computed (*12*). A Fleiss generalized kappa and associated 95% confidence interval was used to assess overall agreement among the 3 readers (*12*).

The data analyses were conducted using SAS® Software, Version 9.4 or higher (IBM, Cary, North Carolina, USA).

RESULTS

Dose-Ranging Study

Table 2 shows the image scoring of the 3 blinded readers as well as the cohort scores for each dose. According to the cohort scores, the 148 MBq (4.0 mCi) and 185 MBq (5.0 mCi) ^{64}Cu-DOTATATE doses displayed superior image quality compared to the 111 MBq (3.0 mCi) dose. Based on the ALARA principle, the 148 MBq (4.0 mCi) dose was selected as the optimal dose for the subsequent pivotal phase III study.

Sensitivity and Specificity (Phase III Primary Objective)

Three readers evaluated the sensitivity and specificity of ^{64}Cu-DOTATATE PET/CT compared with an SOT in 63 evaluable subjects with known or suspected NETs (Table 3). Significant sensitivity and specificity were demonstrated for all readers. Reader 1 had a sensitivity and specificity of 90.9% ($P = 0.0042$) and 96.6% ($P = 0.0042$), respectively; Reader 2 of 90.9% ($P = 0.0042$) and 80.0% ($P = 0.0172$); and Reader 3 of 90.9% ($P = 0.0042$) and 90.0% ($P = 0.0003$). The PPVs of the 3 readers ranged from 83.3% to 96.8%, all NPVs were nearly 90.0%, and accuracy ranged from 85.7% to 93.6%. Two of the 3 readers had point estimates of specificity ≥90.0%, whereas the third had a point-estimate specificity of 80.0% in determining absence of NETs when disease was indeed absent. All readers passed the sensitivity and specificity hypotheses (coprimary effectiveness endpoints with sensitivity >70.0% and specificity >60.0%) testing at a one-sided $\alpha = 0.025$ level of significance.

After the database lock, reasons for failing to detect NETs were reviewed retrospectively, and it was found that SOT reads for 3 subjects were incorrectly recorded as NET-positive ("Disease") instead of NET-negative ("No Disease") by the oncologist who established the SOT. As the objective of the study was not to assess the SOT oncologist's read, rather the performance of the PET/CT scan against true-positive and true-negative NET diagnoses, we also measured "corrected" diagnostic performance parameters that would have been attained if the SOT had been established correctly. Determination of the "corrected" diagnostic performance found that the sensitivity, specificity, PPV, NPV, and accuracy of Readers 1 and 3 would have been 100.0%, 96.8%, 96.7%, 100.0%, and 98.4%, respectively. Reader 2 would have had a 100.0% sensitivity, 81.8% specificity, 83.3% PPV, 100.0% NPV, and 90.5% accuracy.

Majority-read Imaging Performance, Predictive Value, and Determination of Metastatic Versus Localized Disease (Secondary Objectives)

One of the ^{64}Cu-DOTATATE PET/CT scans for Reader 1 was not evaluable due to breathing artifacts. Therefore, secondary objectives were obtained with 62 subjects. According to the SOT, 29 subjects were NET-negative and 33 were NET-positive. On the basis of the ^{64}Cu-DOTATATE PET/CT imaging, the majority read classified 31 subjects as NET-positive and 31 as NET-negative, translating to significant diagnostic performance. Sensitivity, specificity, PPV, NPV, and accuracy for the majority read were 90.9% ($P = 0.0042$), 96.6% ($P < 0.0001$), 96.8%, 90.3%, and 93.6%, respectively (Table 3). Using a "corrected" SOT, the per patient majority read sensitivity, specificity, PPV, NPV, and accuracy were 100.0% ($P = 0.0002$), 96.8% ($P < 0.0001$), 96.7%, 100.0%, and 98.4%. Further, the ability to differentiate between metastatic and localized disease with ^{64}Cu-DOTATATE PET/CT revealed a majority read of 100.0% sensitivity and 100.0% specificity.

Inter- and Intra-Reader Agreement (Tertiary Objectives)

Overall, the 3 readers demonstrated a substantial degree of inter-reader agreement (kappa = 0.7664), with Readers 1 and 3 having almost perfect agreement (kappa = 0.8710) among the reader pairs. Table 4 presents a summary of the inter-reader agreement for assessment of ^{64}Cu-DOTATATE PET/CT imaging.

For the intra-reader variability, Readers 1 and 3 demonstrated perfect intra-reader agreement upon image re-read (kappa = 1.0000). Table 5 presents a summary of intra-reader agreement of ^{64}Cu-DOTATATE PET/CT imaging.

Safety

Overall, 7.9% (5/63) of subjects experienced a total of 9 mild-to-moderate adverse events, with 8 adverse events deemed by the investigator as "probably" not related to ^{64}Cu-DOTATATE administration. Adverse events "probably" not related to administration of ^{64}Cu-DOTATATE included 1 case each of nausea (Grade 1), headache (Grade 1), syncope (Grade 2), melanoderma (Grade 1), and flushing (Grade 1) and 2 cases of vomiting (both Grade 1). One subject (1.6%) experienced Grade 2 hypertension that was determined by the investigator to be "definitely" not related to administration of ^{64}Cu-DOTATATE. No subject experienced a serious adverse event.

No clinically significant changes from baseline in mean serum chemistry, hematology values, or vital signs (5, 10, 30, or 60 minutes postinjection or at discharge) occurred. Additionally, no changes were observed in electrocardiogram parameters from baseline to 1-hour postinjection of ^{64}Cu-DOTATATE.

DISCUSSION

The current study demonstrated that PET/CT imaging with 148 MBq ^{64}Cu-DOTATATE is a safe and highly accurate approach to the diagnosis of NET-positive patients with SSTR-expressing tumors. We also showed that excellent quality images can be rendered (Fig. 1 and Fig. 2) to facilitate high inter-reader and intra-reader agreement on the presence or absence of metastatic or localized disease. The safety profile of ^{64}Cu-DOTATATE proved excellent in our study, with no serious adverse events or adverse events related to ^{64}Cu-DOTATATE.

The NET-positive misread by the SOT oncologist must be considered to accurately gauge the diagnostic performance of ^{64}Cu-DOTATATE in this study. This might have been avoided with use of multiple oncologists or a multidisciplinary team to establish the SOT. However, we believe that assessment of the "corrected" individual and majority-read values provides an accurate evaluation of the diagnostic performance of ^{64}Cu-DOTATATE.

Despite their previous use in PET radiopharmaceuticals, few studies have investigated ^{64}Cu-labeled ligands for PET imaging of NETs (*7*-*9*). Of the available studies in patients with NETs, the first-in-human study compared ^{64}Cu-DOTATATE PET/CT with ^{111}In-DTPA-octreotide SPECT/CT imaging in 14 patients with histopathologically confirmed NETs (*9*). Investigators reported excellent image quality, reduced radiation burden (6.3 vs 12.0 mSv), and detection of additional lesions in 42.9% (6/14) of patients with ^{64}Cu-DOTATATE (*9*). In a prospective, head-to-head study of 112 patients with histopathologically confirmed NETs, ^{64}Cu-DOTATATE PET/CT identified more true-positive NET patients, lesions, and additional organs with disease involvement than ^{111}In-DTPA-octreotide SPECT/CT (*8*). More recently, Johnbeck et al. showed that on a per patient basis ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC displayed the same 100% sensitivity, 90% specificity, 98% PPV, and 100% NPV (*7*). However, on a per lesion basis, ^{64}Cu-DOTATATE correctly identified more true-positive discordant lesions than ^{68}Ga-DOTATOC (83% vs 17%) (*7*). Investigators attributed these findings to the physical properties of ^{64}Cu-DOTATATE versus ^{68}Ga-DOTATOC. In particular, investigators noted that the shorter positron range of ^{64}Cu-DOTATATE likely translated to better spatial resolution, improved image quality, and superior detection of smaller lesions (*7*).

Unlike the aforementioned studies, which used higher radiotracer doses, we conducted a dose-ranging study and found that a lower (than previously published) ^{64}Cu-DOTATATE dose

of 148 MBq (4.2–5.1 mSv) provides diagnostic-quality PET/CT images. Our results are encouraging, as the radiation burden associated with the 148 MBq ^{64}Cu-DOTATATE dose is lower than that of ^{111}In-DTPA-octreotide and similar to ^{68}Ga-labeled radiopharmaceuticals at the commercially available ~185 MBq (5 mCi) dose (*7*-*9*).

A strength of our study is the inclusion of many (21/63) NET-negative healthy volunteers. The pre-established 2:1 (positive:negative) ratio translates to a more robust determination of diagnostic performance, which was bolstered by the high inter-reader (kappa = 0.76) and intra-reader agreement (kappa = 1.0 for 2 of the 3 readers). In diagnostic performance studies using only NET-positive patients, long-term follow-up is typically necessary to confirm initial NET-positive lesions as true-positives. The use of a large population of healthy volunteers and SOT eliminated the need for long-term follow-up and provided a more robust evaluation of specificity and NPV.

^{64}Cu-DOTATATE offers several potentially practical advantages over ^{68}Ga-DOTATATE. First, ^{64}Cu-DOTATATE is a cyclotron-produced positron emitter that can be manufactured in large-scale with a well-controlled process at a centralized location. The production of ^{68}Ga-DOTATATE, by contrast, is largely limited to major tertiary radiopharmacies with varying levels of quality control. The centralized and large-scale production of ^{64}Cu-DOTATATE may ensure greater quality control and eliminate the need for a ^{68}Ge/^{68}Ga generator locally. Second, the longer half-life of ^{64}Cu-DOTATATE versus ^{68}Ga-DOTATATE (12.7 vs 1.1 h) and centralized production may allow for wider geographical distribution, more flexible patient scheduling, and less strain for nuclear medicine technologists who must coordinate radio-isotope delivery with patient and scanner availability. Third, the shorter positron range of ^{64}Cu-DOTATATE and associated improvements in resolution may permit the detection of more

and/or smaller lesions than those observed with ^{68}Ga-DOTATATE. Fourth, the longer half-life of ^{64}Cu-DOTATATE also may provide therapeutic benefits. For example, ^{64}Cu-DOTATATE may permit delayed serial imaging with important implications for personalized dosimetry planning in PRRT, as well as aid in clarifying suspect findings observed on initial scans. A recent study suggests that the 12.7-hour half-life of ^{64}Cu-DOTATATE may improve radioguided surgery using a dedicated positron hand-held probe (*13*).

CONCLUSION

^{64}Cu-DOTATATE PET/CT is a safe and highly accurate imaging technique to detect SSTR-expressing NETs. In addition, diagnostic performance for ^{64}Cu-DOTATATE PET/CT is highly reproducible and accurately identifies metastatic versus localized lesions. The longer half-life, lower positron energy, and lower positron range of ^{64}Cu-DOTATATE compared with ^{68}Ga-labeled compounds makes ^{64}Cu-DOTATATE a user-friendly radiopharmaceutical with the potential for practical and logistic benefits over currently approved radionuclide tracers used to identify patients with NETs.

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KEY POINTS

Question (one sentence)**:** Is ^{64}Cu-DOTATATE PET/CT a potential alternative to ^{68}Ga-labeled SSTR tracers for imaging in patients with NETs?

Pertinent findings (one or two sentences)**:** The current study was the first US phase III, prospective, reader-blinded clinical trial and was conducted in a total of 63 subjects—42 patients with suspected or confirmed SSTR-positive NETs and 21 known true-negative healthy volunteers. The study confirmed an ALARA optimal dose for diagnostic-quality images at a lower (than previously published) radiation burden, which was safe, highly reproducible, and accurate for determining the absence or presence of localized or metastatic NET disease.

IMPLICATIONS FOR PATIENT CARE (one sentence)**:** ^{64}Cu-DOTATATE PET/CT constitutes a viable, highly accurate imaging modality that may improve detection of NET lesions and increase access to high-quality PET/CT.

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FIGURES

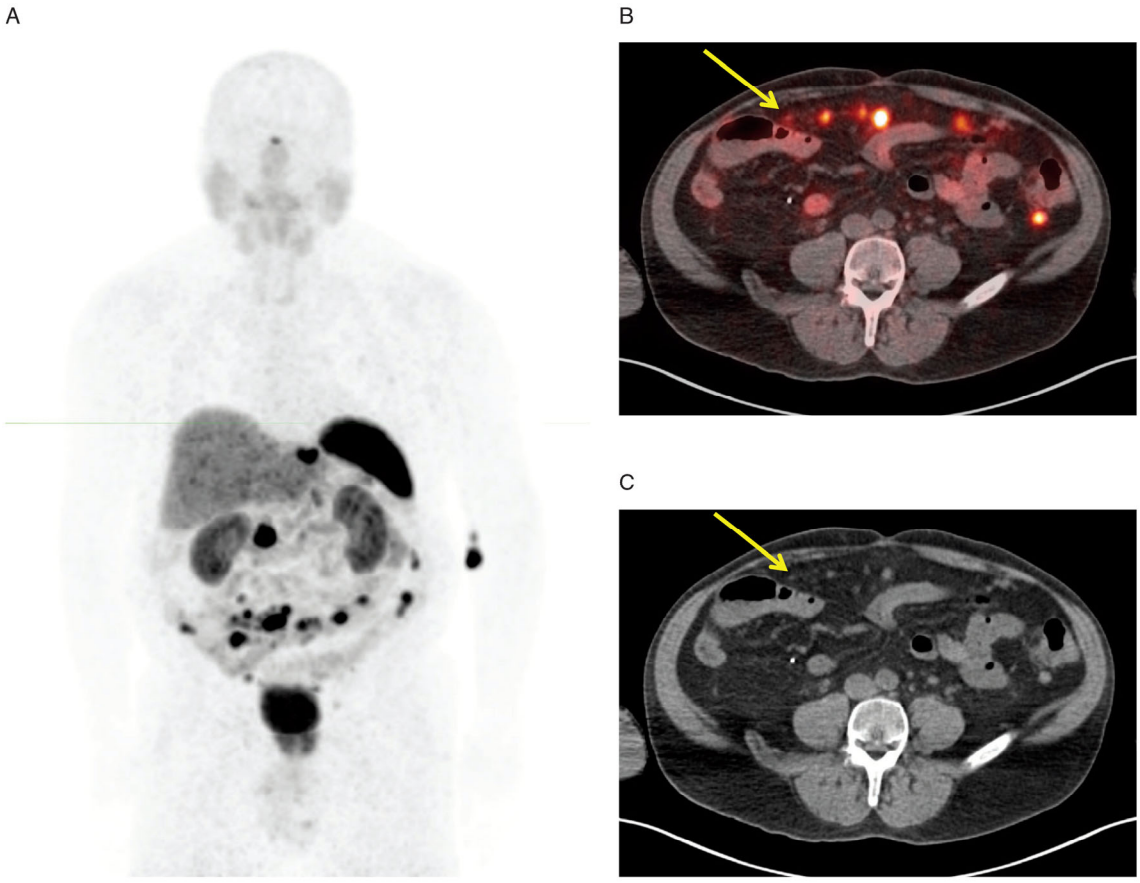

FIGURE 1. Maximum intensity projection image of a patient with metastatic small bowel carcinoid tumor (A). A small omental (yellow arrow) and peritoneal tumor implants are visible in the fused PET/CT (B) and corresponding CT (C) images. CT = computed tomography; PET = positron emission tomography.

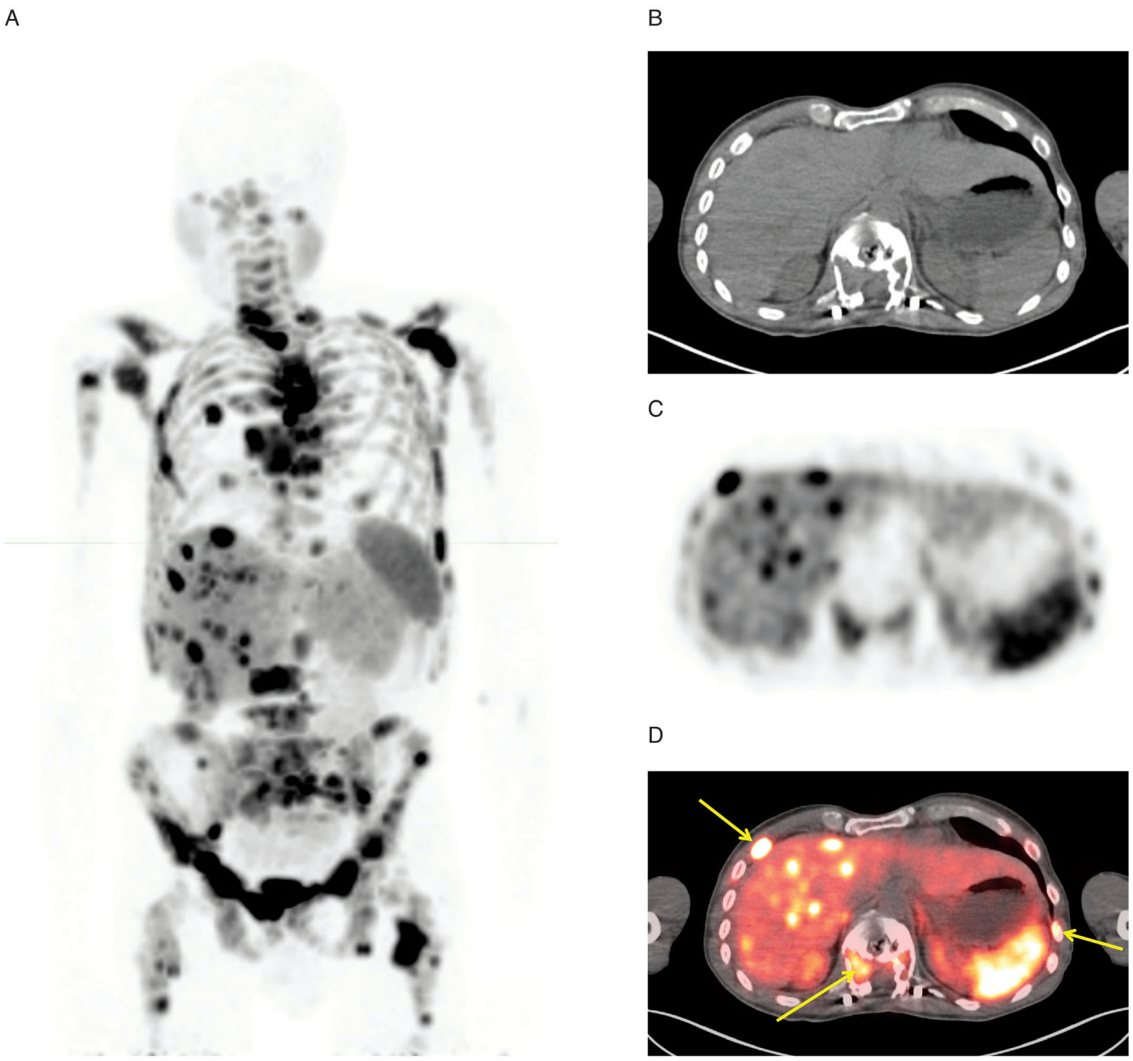

FIGURE 2. Maximum intensity projection image of a patient with metastatic bronchial carcinoid and extensive metastatic disease including multiple small liver metastases (A). Corresponding CT image (B), PET (C), and fused PET/CT showing multiple bone metastases (yellow arrows; D). CT = computed tomography; PET = positron emission tomography.

TABLES

TABLE 1

Demographics and Baseline Characteristics (Safety Population)

	Dose-Ranging Study (N = 12)	**Phase III Study (N = 63)**
Age (years), n		
Mean (SD)	62.0 (12.7)	54.4 (15.7)
Median (min, max)	59.5 (44.0, 83.0)	54.0 (25.0, 82.0)
Height (cm), n		
Mean (SD)	172.1 (9.9)	171.9 (11.43)
Median (min, max)	171.4 (157.4, 193.0)	172.7 (147.3, 199.9)
Weight (kg), n		
Mean (SD)	72.4 (19.8)	84.3 (21.2)
Median (min, max)	69.8 (45.3, 113.4)	80.7 (51.7, 148.3)
Gender, n (%)		
Male	5 (41.7)	28 (44.4)
Female	7 (58.3)	35 (55.6)
Race, n (%)		
American Indian or Alaska Native	0 (0)	0 (0)
Asian	0 (0)	2 (3.2)
Black or African American	0 (0)	6 (9.5)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)
White	12 (100.0)	54 (85.7)
Other	0 (0)	1 (1.6)
Ethnicity, n (%)		
Hispanic or Latino	0 (0)	11 (17.5)
Not Hispanic or Latino	12 (100.0)	52 (82.5)
Unknown	0 (0)	0 (0)
Not Reported	0 (0)	0 (0)

SD = standard deviation.

TABLE 2

Image Scoring of the Dose-Ranging Study

Dosing Group	Reader 1	Reader 2	Reader 3	Average Image Subject Score	Cohort Score
111 MBq (3 mCi)	2.0	2.0	2.0	2.0	5.4
	2.0	0	1.0	1.0	
	1.0	1.0	0	0.7	
	2.0	2.0	1.0	1.7	
148 MBq (4 mCi)	2.0	2.0	1.0	1.7	7.1
	2.0	2.0	1.0	1.7	
	2.0	2.0	1.0	1.7	
	2.0	2.0	2.0	2.0	
185 MBq (5 mCi)	1.0	1.0	1.0	1.0	7.0
	2.0	2.0	2.0	2.0	
	2.0	2.0	2.0	2.0	
	2.0	2.0	2.0	2.0	

Image scoring: 0 = inadequate (images look grainy with poor delineation of lesions); 1 = questionable (images are clear but lesion delineation is suboptimal and small lesions [1 cm] are hard to assess); 2 = acceptable (images are clear, large and small lesion delineation is possible).

Cohort scores were calculated by adding up the average image subject scores in each dosing group.

TABLE 3

Individual Reader and Majority Reads for ^{64}Cu-DOTATATE PET/CT Imaging Versus SOT

Parameters	Sensitivity	Specificity	PPV*	NPV*	Accuracy*
Reader 1	0.9091 (0.7643, 0.9686) [0.0042]	0.9655 (0.8282, 0.9939) [0.0042]	0.9677 (0.8381, 0.9943)	0.9032 (0.7510, 0.9665)	0.9355 (0.8455, 0.9746)
Reader 2	0.9091 (0.7643, 0.9686) [0.0042]	0.8000 (0.6269, 0.9049) [0.0172]	0.8333 (0.6811, 0.9213)	0.8889 (0.7194, 0.9615)	0.8571 (0.7503, 0.9230)
Reader 3	0.9091 (0.7643, 0.9686) [0.0042]	0.9000 (0.7438, 0.9654) [0.0003]	0.9091 (0.7643, 0.9686]	0.9000 (0.7438, 0.9654)	0.9048 (0.8074, 0.9556)
Majority Read	0.9091 (0.7643, 0.9686) [0.0042]	0.9655 (0.8282, 0.9939) [<0.0001]	0.9677 (0.8381, 0.9943)	0.9032 (0.7510, 0.9665)	0.9355 (0.8455, 0.9746)
"Corrected" Majority Read	1.0000 (0.8865, 1.0000) [0.0002]	0.9680 (0.8426, 0.9945) [<0.0001]	0.9670 (0.8381, 0.9943)	1.0000 (0.8928, 1.0000)	0.9840 (0.9141, 0.9971)

*The statistical analysis plan included a testable hypothesis for the coprimary endpoints (ie, sensitivity and specificity). Thus, *P* values were calculated for sensitivity and specificity, and not PPV, NPV, and accuracy.

Confidence intervals are in parentheses, and *P* values are in brackets ($P < 0.05$ are considered statistically significant). CT = computed tomography; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; SOT = standard of truth.

TABLE 4
Summary of Inter-Reader Agreement for Assessment of ^{64}Cu-DOTATATE PET/CT Imaging

Reader Pair	N	Kappa (SE)	95% CI on Kappa
1 vs 2	62*	0.7419 (0.0844)	(0.5764, 0.9074)
1 vs 3	62*	0.8710 (0.0623)	(0.7489, 0.9930)
2 vs 3	63	0.7123 (0.0883)	(0.5392, 0.8855)
Overall	63	0.7664 (0.0732)	(0.6229, 0.9099)

*Reader 1 could not evaluate the ^{64}Cu-DOTATATE PET/CT of 1 subject due to image artifact caused by breathing motion. CI = confidence interval; CT = computed tomography; PET = positron emission tomography; SE = standard error.

TABLE 5

Intra-Reader Agreement of ^{64}Cu-DOTATATE PET/CT Imaging

Reader	Parameter	Estimate	95% CI
1	Kappa	1.0000	(1.0000, 1.0000)
	Uncorrected agreement	1.0000	(0.5904, 1.0000)
2	Kappa	0.5333	(0.0596, 1.0000)
	Uncorrected agreement	0.7143	(0.2904, 0.9633)
3	Kappa	1.0000	(1.0000, 1.0000)
	Uncorrected agreement	1.0000	(0.5904, 1.0000)

CI = confidence interval; CT = computed tomography; PET = positron emission tomography.