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Date of Request: 03Sep2020
NCCN Guidelines Panel: Neuroendocrine Tumors Panel

On behalf of Curium, I respectfully submit this amended request from our original 07Oct2019 submission to the National Comprehensive Cancer Network (NCCN) Neuroendocrine Tumors Panel due to the Guidelines changing since our last request. We are asking to review the previously and newly added enclosed data for addition of 64Cu-dotatate PET/CT (SSR-PET/CT) and 64Cu-dotatate PET/MRI (SSR-PET/MRI) in the Principles of Imaging (NE-B) section. We are also asking to include copper Cu 64 dotatate injection as an example of PET somatostatin receptor-based imaging by including it in the "eg" for SSR based imaging PET/CT and PET/MRI to denote an example for the NCCN Clinical Practice Guidelines in Oncology Neuroendocrine and Adrenal Tumors version 2.2020-July 24, 2020. I would considerately ask that this is also updated in similar spirit for the corresponding NCCN Evidence Blocks guideline Version 2.2020 August 10, 2020 as well as the NCCN Guidelines for Patients for Neuroendocrine Tumors 2018.

Specific Changes: For all locations, replacing the example of somatostatin receptor-based imaging of:

1. *SSR-based imaging (eg, 68 Ga-dotatate imaging preferred [PET/CT or PET/MRI] or SSR scintigraphy)* with

   *SSR-based imaging (eg, 68 Ga or 64Cu-dotatate imaging preferred [PET/CT or PET/MRI] or SSR scintigraphy))*

And for Principles of Imaging (NE-B), Functional Imaging, SSR-based imaging options include: replace the below:

2. *68Ga-dotatate PET/CT (SSR-PET/CT)*
   *68Ga-dotatate PET/MRI (SSR-PET/MRI)* with

   *68Ga or 64Cu-dotatate PET/CT (SSR-PET/CT)*
   *68Ga or 64Cu-dotatate PET/MRI (SSR-PET/MRI)...*

FDA Clearance: copper Cu 64 dotatate injection for intravenous use was approved on 03Sep2020 and approval letter is enclosed.

Rationale: While PET somatostatin imaging is the preferred imaging modality over SPECT imaging when available, Gallium-68 dotatate (68Ga-dotatate) is no longer the only moiety that fulfils that definition. It is expected that copper Cu 64 dotatate injection will be widely available to also fulfil that definition and has the same ligand as the current listed drug.

In addition to the previously submitted articles and Clinical Summary in support of this proposed changes listed below:.

1. Pfeifer A, Knigge U, Mortensen J, et al. Clinical PET of neuroendocrine tumors using 64Cu-DOTATATE: first-in-humans study. J Nucl Med. 2012;53:1207–1215.
2. Pfeifer A, Knigge U, Binderup T, et al. 64Cu-DOTATATE PET for neuroendocrine tumors: a prospective head-to-head comparison with 111In-DTPA-octreotide in 112 patients. J Nucl Med. 2015;56:847–854.
3. Johnbeck C, Knigge U, Loft A, et al. Head-to-Head Comparison of 64Cu-DOTATATE and 68Ga-DOTATOC PET/CT: A Prospective Study of 59 Patients with Neuroendocrine Tumors. J Nucl Med. 2017;58:451-457
4. 2.5 Clinical Overview NDA Submission of 64Cu-DOTATATE
5. Kjaer A, Binderup T, Johnbeck C, et al. (2019, October) *$^{64}$Cu DOTATATE somatostatin receptor imaging in neuroendocrine tumor patients: experience from more than 1,200 patients*. Poster session presented at the Annual Symposium of the North American Neuroendocrine Tumor Society, Boston, MA.

The below newly added articles are being submitted as well in addition to the FDA approval letter and Prescribing Information:

6. Carlsen E, Johnbeck C, Binderup T, et al. *$^{64}$Cu -DOTATATE PET/CT and prediction of overall and progression free survival in patients with neuroendocrine neoplasms*. J Nucl Med. Published ahead of print 28Feb2020
7. Loft M, Carlsen E, Johnbeck C, et al. *$^{64}$Cu-DOTATATE PET in Patients with Neuroendocrine Neoplasms: Prospective, Head-to-Head Comparison of Imaging at 1 Hour and 3 Hours Post-Injection* . J Nucl Med. Published ahead of print 22May2020
8. Delpassand E, Ranganathan D, Wagh N, et al. *$^{64}$Cu* -DOTATATE PET/CT for Imaging Patients with Known or Suspected Somatostatin Receptor–Positive Neuroendocrine Tumors: Results of the First U.S. Prospective, Reader-Masked Clinical Trial. J Nucl Med. 2020;61:890–896
9. FDA Approval Letter with enclosed prescribing information

Thank you for your time and consideration. Sincerely,

Digitally signed by Fred Gattas, Pharm.D., BCNP, FAPhA
DN: cn=Fred Gattas, Pharm.D., BCNP, FAPhA, o=Curium, ou=Medical and Safety Affairs, email=Fred.Gattas@curiumpharma.com, c=US
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# $^{64}$Cu-DOTATATE PET/CT and prediction of overall and progression-free survival in patients with neuroendocrine neoplasms

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**Running title:** Prognostication by $^{64}$Cu-DOTATATE PET/CT

**Word count:** 4998 (max 5000)

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## ABSTRACT

Overexpression of somatostatin receptors in patients with neuroendocrine neoplasms (NEN) is utilized for both diagnosis and treatment. Receptor density may reflect tumor differentiation and thus be associated with prognosis. Non-invasive visualization and quantification of somatostatin receptor density is possible by somatostatin receptor imaging (SRI) using positron emission tomography (PET). Recently, we introduced $^{64}$Cu-DOTATATE for SRI and we hypothesized that uptake of this tracer could be associated with overall (OS) and progression-free survival (PFS).

### Methods

We evaluated patients with NEN that had a $^{64}$Cu-DOTATATE PET/CT SRI performed in two prospective studies. Tracer uptake was determined as the maximal standardized uptake value ($SUV_{max}$) for each patient. Kaplan-Meier analysis with log-rank was used to determine the predictive value of $^{64}$Cu-DOTATATE $SUV_{max}$ for OS and PFS. Specificity, sensitivity and accuracy was calculated for prediction of outcome at 24 months after $^{64}$Cu-DOTATATE PET/CT.

### Results

A total of 128 patients with NEN were included and followed for a median of 73 (1-112) months. During follow-up, 112 experienced disease progression and 69 patients died. The optimal cutoff for $^{64}$Cu-DOTATATE $SUV_{max}$ was 43.3 for prediction of PFS with a hazard ratio of 0.56 (95% CI: 0.38-0.84) for patients with $SUV_{max} > 43.3$. However, no significant cutoff was found for prediction of OS. In multiple Cox regression adjusted for age, sex, primary tumor site and tumor grade, the $SUV_{max}$ cutoff hazard ratio was 0.50 (0.32-0.77) for PFS. The accuracy was moderate for predicting PFS (57%) at 24 months after $^{64}$Cu-DOTATATE PET/CT.

### Conclusion

In this first study to report the association of $^{64}$Cu-DOTATATE PET/CT and outcome in patients with NEN, tumor somatostatin receptor density visualized with $^{64}$Cu-DOTATATE PET/CT was prognostic for PFS but not OS. However, the accuracy of prediction of PFS at 24 months after $^{64}$Cu-DOTATATE PET/CT SRI was moderate limiting the value on an individual patient basis.

**Keywords:**

$^{64}$Cu-DOTATATE PET/CT; Maximal standardized uptake value (SUVmax); Neuroendocrine neoplasm; Progression-free survival; Overall survival

## INTRODUCTION

Patients diagnosed with neuroendocrine neoplasms (NEN) have a highly variable survival ranging from a few months to decades (*1*). The origin of NEN are frequently gastro-entero-pancreatic (~75%) or lung (~25%). Gastro-entero-pancreatic NEN are pathologically graded by mitotic rate and proliferation index (Ki-67) in G1 (<3%), G2 (3-20%) and G3 (>20%) and by differentiation in well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinoma (NEC). NEC are further classified as small or large cell type (*2,3*). Lung NEN are pathologically classified as typical or atypical carcinoids, large cell neuroendocrine carcinoma or small cell lung carcinoma. Most patients with NEN have low-grade disease and experience long-term survival (*1*). Treatment is based on resectability, presence of metastases, location of primary tumor and metastases, and histology of tumor biopsies (*4*). However, as evaluation based on histology is prone to sampling error, more precise prognostic methods are needed. Positron emission tomography (PET) allows for a whole-body molecular examination and is well suited for non-invasive longitudinal monitoring of the entire tumor burden. Although $^{18}$F-flourodeoxyglucose (FDG) PET is widely used for cancer imaging and is prognostic in NEN of all grades (*5,6*), it is currently not recommended as a routine in low grade NEN. However, a feature of most NEN is overexpression of somatostatin receptors (SSTR). The SSTR density on the tumor cell surface may reflect the degree of differentiation and proliferative index, i.e. most SSTR on well-differentiated tumors with low proliferation index (*7,8*). SSTR are used as target in somatostatin receptor imaging (SRI), which plays an essential role in diagnosis, treatment decision as well as follow-up of NEN (*9*). The general principle applied involves a radioisotope conjugated via a chelator (e.g. tetraxetan [DOTA]) to a somatostatin analogue (e.g. Tyr$^3$-octreotate [TATE]). In diagnostics, PET tracers ($^{68}$Ga- or $^{64}$Cu-conjugated somatostatin analogues) are used, and for therapy $^{177}$Lu-conjugated somatostatin analogues are used (*10*). PET tracer uptake can be quantified as

standardized uptake value (SUV). Preliminary results in smaller cohorts have indicated that maximal SUV ($SUV_{max}$) in $^{68}$Ga-SRI as a measure of SSTR density is predictive of progression free survival (PFS) in NET (*11-13*). However, the prognostic implications for overall survival (OS) have not previously been reported. We recently introduced $^{64}$Cu labeled DOTATATE for NEN that has excellent image resolution and can be centrally produced due to the long half-life (*14*). Hence, the aim of the present study was to examine in a large cohort the ability of $^{64}$Cu-DOTATATE PET/CT to predict OS and PFS. We hypothesized that increasing lesion $SUV_{max}$ was associated with longer OS and PFS.

## PATIENTS AND METHODS

### Patients

Our group performed two prospective clinical studies with $^{64}$Cu-DOTATATE PET/CT including patients between November 2009 and March 2013 with a planned follow-up study (*15,16*), approved by the Regional Scientific Ethical Committee (reference no. H-D-2008-045), and all participating patients signed an informed consent form. Included patients had histopathologically confirmed NEN and were referred for PET/CT for staging, restaging or follow-up. All scans were reviewed for inclusion in the present follow-up study. If more than one $^{64}$Cu-DOTATATE PET/CT was available for a patient, the earliest scan was used. We excluded patients with no signs of NEN due to previous radical surgery. Thus, only patients with presence of NEN detectable by PET and/or CT were included. Patients were followed and treated with standard of care at the ENETS Neuroendocrine Tumor Center of Excellence Rigshospitalet, Copenhagen, Denmark. Treatment decisions were blinded to the $^{64}$Cu-DOTATATE PET/CT but guided by $^{111}$In-Octreotide scintigraphy (clinical routine throughout the inclusion period). Baseline characteristics collected were age, sex, time of diagnosis, site of primary

tumor, Ki-67 index (%) and World Health Organization (WHO) grade and NEN-specific treatment prior to SRI. Follow-up with diagnostic CT was undertaken biannually or annually. At the discretion of the treating physician, SRI, magnetic resonance imaging and/or ultrasound were also performed during follow-up.

## Radiotracer and Image Acquisition

Radiotracer production, PET/CT image acquisition and reconstruction methodology has been published previously (*14-16*). In short, $^{64}$Cu-DOTATATE was produced in-house and patients had a whole-body PET/CT scan performed 62 ± 1 min (range, 43-99 min) after injection of 202.7 ± 1.0 MBq (range, 174-245 MBq) $^{64}$Cu-DOTATATE. A Siemens Biograph 40 or 64 TruePoint PET/CT was used and all images were reconstructed with the same reconstruction parameters and algorithm (TrueX; Siemens Medical Solutions). To ensure quantitatively accurate measurements between the different PET/CT scanners, we perform a quality control every 2 weeks, testing they are calibrated to measure within our acceptance range (5%). Furthermore, a diagnostic CT scan with iodine intravenous contrast was performed before the PET scan unless contraindicated.

## Image Analysis

An experienced board certified nuclear medicine physician together with an experienced board certified radiologist analyzed side-by-side the PET/CT scans. SUV was calculated as decay-corrected measured radioactivity concentration/(injected activity/body weight). The maximal SUV was obtained by drawing spherical volumes encompassing the entire lesion. Within each lesion site (divided into regions

or groups: lung, pancreas, liver, intestines, bones, lymph nodes, and other) the maximal SUV was noted. For each patient, the maximal $SUV_{max}$ obtained was used as the predictor variable, and for simplicity referred to as $SUV_{max}$ in this article.

## Endpoints

Follow-up was performed on March 28th 2019. CT routine images and or magnetic resonance imaging were used for evaluation of PFS in accordance with Response Evaluation Criteria in Solid Tumors v. 1.1 (*17*). PFS was calculated as time from $^{64}$Cu-DOTATATE PET/CT to, if any, progression or tumor-related death. If no progression or tumor-related death occurred within the follow-up, the patient was censored at the time of last available diagnostic imaging. OS was calculated as time from $^{64}$Cu-DOTATATE PET/CT to death by any cause. Patients alive at follow-up were censored to the day of follow-up, i.e. March 28th 2019.

## Statistics

Continuous variables are reported as mean and standard error of mean (SEM) or median and range. Independent t-test and one-way ANOVA with post-hoc analysis by Tukey were used for comparison of means. Kaplan Meier analyses were used for estimation of time to outcome (PFS and OS). The optimal cutoff for $SUV_{max}$ was determined by log-rank test, as the point yielding the most significant log rank test split. This was done using the Cutoff Finder web application (*18*). Multiple Cox regression analyses for outcome with predictor variables being age, sex, primary tumor site, $SUV_{max}$ and WHO grade were performed. Furthermore, specificity, sensitivity and accuracy in predicting outcome (PFS

and OS) at 24 months by the determined $SUV_{max}$ cutoff was calculated. The time cutoff of 24 months after the $^{64}$Cu-DOTATATE PET/CT scan was chosen to put the performance of prognostication into a clinically relevant timeline, where most patients undergo PET/CT biannually or annually, while some have PET/CT every other year. A p-value<0.05 was considered statistically significant. R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used for the analyses.

## RESULTS

### Patients

A total of 172 $^{64}$Cu-DOTATATE PET/CT scans were performed in relations to the two aforementioned studies; hereof 25 patients participated in both studies. In the 147 unique patients scanned, 128 patients had NEN present at the time of scan and were thus included in the study; baseline characteristics in Table 1.

### $^{64}$Cu-DOTATATE $SUV_{max}$

Mean $SUV_{max}$ ± SEM of the primary tumor or metastasis was 62.2 ± 3.3 in the entire cohort; values of subgroups are reported in Table 2. A tendency of lower $SUV_{max}$ was observed for patients with a poor outcome (deceased [p=0.06] or progressive disease [p=0.17]) at the defined 24 months cutoff after $^{64}$Cu-DOTATATE PET/CT. $SUV_{max}$ differed significantly according to primary tumor site with higher $SUV_{max}$ values for lesions originating from pancreas as compared to lesions originating from gastrointestinal sites. No significant difference in $SUV_{max}$ was observed for patients with G1 vs. G2 vs. G3 NEN, see Figure 1.

## Prediction of OS and PFS

After the $^{64}$Cu-DOTATATE scan, patients were followed for a median of 73 (range 1-112) months, 112 had progressive disease and 69 patients died during follow-up. Median PFS was 23 (95% CI: 19-30) months and median OS was 85 (95 % CI: 66 – upper limit not reached) months. Applying the cutoff finder method (*18*), a cutoff of $SUV_{max}$ 43.3 yielded a hazard ratio of 0.56 (0.38-0.84) for prediction of PFS (reference $SUV_{max} \leq 43.3$). No significant cutoff for prediction of OS was identified, thus the 43.3 cutoff was used in the Kaplan Meier plot for OS, see Figure 2-3. A significantly higher risk was found for WHO G3 vs. G2 and G1 for OS and PFS. However, no significant difference was found for G1 vs. G2, see Figure 4.

In a multiple Cox regression analysis with outcome being PFS, both the identified $SUV_{max}$ cutoff and WHO grade were significantly associated with PFS, whilst age, sex and primary tumor site were not. In a multiple Cox regression analysis with outcome being OS, only WHO grade and age were significantly associated with OS, see Figure 5.

Prediction of PFS/OS 24 months after $^{64}$Cu-DOTATATE PET/CT had a sensitivity of 39/41%, specificity of 76/71% and accuracy of 57/64%, respectively.

## DISCUSSION

This is the first study to report the association between $^{64}$Cu-DOTATATE PET/CT and outcome in patients with NEN. The main finding of our study in a cohort of 128 patients with NEN of all WHO grades and followed for up to more than 9 years was that $^{64}$Cu-DOTATATE $SUV_{max}$ in tumor lesions

was significantly associated with PFS, but not OS. A $^{64}$Cu-DOTATATE $SUV_{max}$ above 43.3 was associated with only half the likelihood of progression (hazard ratio: 0.56; 95% CI: 0.38-0.84) compared to patients with a $^{64}$Cu-DOTATATE $SUV_{max}$ below or equal to 43.3.

SRI, by $^{68}$Ga or $^{64}$Cu conjugated somatostatin analogues, is regarded key in initial diagnosis, staging, follow-up and patient selection for PRRT in NET patients (*19,20*). Addition of PET to CT increases both sensitivity and specificity of NET detection (*21*). Several PET tracers exist, and in general they all show high sensitivity and specificity (*21*). In a head-to-head comparison of $^{64}$Cu-DOTATATE vs. $^{68}$Ga-DOTATOC, we showed that $^{64}$Cu-DOTATATE identified significantly more true lesions than $^{68}$Ga-DOTATOC (*16*). Contrary, SRI is not routinely performed in patients with NEC due to lower sensitivity. In patients with NEC, $^{18}$F-FDG is often used to visualize the increased glucose metabolism in tumor lesions (*22*).

Determination of Ki-67 index in tissue samples is essential in the WHO classification of NEN and has great implications on management of patient treatment. However, as histology is prone to sampling error, methods for whole-body examinations are needed. Furthermore, since most patients with NEN experience long-term survival, methods that allow for easy reexaminations are required. SRI is routinely performed in patients with NET at time of diagnosis and for follow-up evaluations. To the best of our knowledge, studies on prediction of OS based on SRI $SUV_{max}$ have not been reported so far. Previously, it has been reported that $^{68}$Ga-DOTANOC $SUV_{max}$ (*11,12*) and $^{68}$Ga-DOTATATE $SUV_{max}$ (*13*) are predictive for PFS. Our findings confirm these observations in a substantially larger cohort (128 vs. 46/43/30 patients). However, the specific cutoff value varies between the studies, which may have several explanations. Firstly, the study populations varied in regards to origin of primary NEN where one study only had pancreatic tumors (*11*), one study had only ileal tumors (*13*) and one study included primarily pancreatic tumors (*12*). In comparison, our cohort had more patients with primary

gastrointestinal tumors than pancreatic tumors, and included also patients with unknown primary NEN and lung NEN. Our study confirmed the previous finding that primary pancreatic NENs have higher $SUV_{max}$ than gastrointestinal primary tumors, which may affect the obtained cutoff value (*12*). Secondly, the use of different PET isotopes and somatostatin analogues may affect the specific cutoff value. The $^{64}$Cu-DOTATATE $SUV_{max}$ values reported here were greater than what has been reported for $^{68}$Ga-DOTANOC and $^{68}$Ga-DOTATATE (*23,24*). This was also evident in a previous head-to-head comparison of $^{64}$Cu-DOTATATE and $^{68}$Ga-DOTATOC, where $SUV_{max}$ was higher for $^{64}$Cu-DOTATATE (*16*). Collectively, the predictive value of SRI by either $^{68}$Ga or $^{64}$Cu conjugated somatostatin analogue for PFS are likely to be similar for the different SRI tracers, i.e. a class effect.

Having demonstrated the predictive value of $^{64}$Cu-DOTATATE $SUV_{max}$ for PFS, the question arises whether this can be used on an individual basis? Using the identified optimal $SUV_{max}$ cut-off of 43.3 for prediction of PFS at 24 months, a moderate accuracy of 57% was found. The previous studies also reported moderate to low accuracy in prediction of PFS on an individual patient level (*11-13*).

In contrast to what was the case for PFS, our study could not demonstrate that $^{64}$Cu-DOTATATE $SUV_{max}$ was predictive for OS. Currently, there are no other studies that have looked into SRI and OS. We would have expected that inclusion of NEN G3, which have a substantially poorer prognosis and lower SSTR expression, would have revealed an association between $^{64}$Cu-DOTATATE $SUV_{max}$ and OS. However, the NEN G3 only made up a small part of the study population and therefore we may have been underpowered to show the relation regarding OS.

Supporting the prognostic implications of SSTR are histological examinations with immunohistochemistry of NEN samples reporting variations in density of SSTR expression according

to tumor proliferation and differentiation (*7,8,25-27*). SRI $SUV_{max}$ measured in biopsied lesions show close correlation with SSTR2 gene expression (*28*) and SSTR expression assed with immunohistochemistry (*29,30*). In well differentiated tumors, the density of SSTR may be greater compared to poorly differentiated NEN, and SSTR density has been associated with survival (*25,31,32*). However, a large dataset from 163 patients with NEN Ki-67 > 20%, shows that strong SSTR2a expression is present in a great proportion of patients, especially in pancreatic NEC and SSTR2a density was not prognostic (*33*). Hence, the notion that SSTR is a trait restricted to low grade NET, and thus an indicator of differentiation, may not hold true.

Ideally, the minimum SUV should be applied in SRI, as the tumor or metastasis with the lowest SSTR density, i.e. the most dedifferentiated part of the cancer, would then theoretically become the predictor for outcome. However, the accuracy and reproducibility of such a measure is questionable, and in a previous attempt, minimum SUV was not predictive of PFS (*13*). With $SUV_{max}$ the greatest SSTR density is reported, and therefore the prediction is likely based on the most differentiated tumor area, omitting more dedifferentiated areas. However, it is possible that there is a correlation between the minimum and maximal SUV, and $SUV_{max}$ is the only realistic measure to obtain in a reproducible way in everyday practice. Other aspects of SRI may be exploited, e.g. a quantitative measure of the total tumor burden based on SRI has also been reported as prognostic for PFS (*34*) . In general, a greater use of the vast information embedded in SRI is warranted.

An alternative to SRI for prognostication in NEN could be $^{18}$F-FDG PET/CT. The tracer reflects glucose uptake, and due to the Warburg effect in tumors cells leading to greatly increased glucose metabolism, a high $SUV_{max}$ is seen in tumors with high glycolytic activity. A strong correlation between $^{18}$F-FDG tumor uptake and prognosis in patients with NEN has been reported (*5,6*), where patients with $^{18}$F-FDG avid tumor lesions have a markedly worse prognosis (hazard ratio of

approximately 10 for both PFS and OS). However, compared to $^{18}$F-FDG, the advantage of SRI prognostication is the availability in almost all NET patients. In this cohort, 12 of 128 patients had $^{18}$F-FDG PET/CT performed within 100 days of the $^{64}$Cu-DOTATATE PET/CT, and we therefore abstained from comparative analysis.

## Limitations

The patient population is a representative population at a NET center. Accordingly, patients may be anything from newly diagnosed to heavily pretreated. While SRI is widely used for NET, $^{18}$F-FDG PET/CT is preferred for high grade NEN (*20*). Therefore, our cohort included relatively few patients with high grade NEN, which may have limited the study's ability to investigate the hypothesized inverse correlation between SRI and OS. Classification of high grade NEN has changed considerably since the patients in this study were included, hence the distinction between NET G3 and NEC (small and large cell) was not available, however only 6 patients had Ki-67% > 20% making further subgrouping of limited value.

## CONCLUSION

In conclusion, $^{64}$Cu-DOTATATE PET/CT $SUV_{max}$ in tumor or metastases was predictive of PFS in our large cohort of 128 patients with NEN that were followed for up to more than 9 years. However, the accuracy of predicting PFS for the individual patient was modest. Regarding OS, we found no predictive value of SRI. Compared to $^{18}$F-FDG PET/CT that has been shown strongly prognostic (PFS and OS) across the NEN grades, there seems little or no role for SRI in individual patient

prognostication. This does not rule out potential prognostic value of SRI when used in predicting outcome of SSTR targeted therapies as PRRT.

## DISCLOSURE

Andreas Kjaer and Ulrich Knigge are inventors on a filed patent application: "PET tracer for imaging of neuroendocrine tumors" (WO 2013029616 A1).

## ACKNOWLEDGEMENTS

We are grateful to the staff at the Department of Clinical Physiology, Nuclear Medicine, and PET for help in providing the PET tracers and performing the PET/CT studies.

## KEY POINTS

**QUESTION:** Is $^{64}$Cu-DOTATATE tumor uptake on PET/CT associated with prognosis in patients with neuroendocrine neoplasms?

**PERTINENT FINDINGS:** Patients with higher tracer uptake had a significantly lower risk of progression, but no significant association with survival was evident. However, the accuracy of predicting prognosis for the individual patient was modest.

**IMPLICATIONS FOR PATIENT CARE:** A high $SUV_{max}$ of $^{64}$Cu-DOTATATE PET/CT is predictive of a longer progression-free survival. However, on an individual patient basis the value

seems limited. Nevertheless, $^{64}$Cu-DOTATATE $SUV_{max}$ have value on an individual basis in predicting outcome of peptide receptor radionuclide therapy.

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## TABLE 1: Baseline characteristics of 128 patients with neuroendocrine neoplasms

| Characteristics | | Value |
|---|---|---|
| Age, years (median [range]) | | 63 [29, 83] |
| Male/Female (%) | | 72/56 (56/44) |
| Time from diagnosis to scan, months (median [range]) | | 18 [0, 208] |
| Primary tumor site (%) | | |
| | Lung | 7 (5) |
| | Unknown primary NEN | 23 (18) |
| | Gastric | 1 (1) |
| | Small intestine | 60 (47) |
| | Pancreas | 25 (20) |
| | Cecum | 8 (6) |
| | Extrahepatic biliary tract | 2 (2) |
| | Esophagus | 1 (1) |
| | Other | 1 (1) |
| Primary tumor site, grouped (%) | | |
| | Lung | 7 (5) |
| | Unknown primary NEN | 23 (18) |
| | Gastrointestinal * | 73 (57) |
| | Pancreas | 25 (20) |
| Ki67 index, % (median [range]) | | 5 [1, 100] |
| WHO grading (%) | | |
| | G1 | 31 (26) |
| | G2 | 84 (69) |
| | G3 | 6 (5) |
| Treatment before $^{64}$Cu-DOTATATE PET/CT (%) † | | |
| | No treatment | 18 (14) |
| | Localized treatment(s) | 13 (10) |
| | Systemic treatment(s) | 43 (34) |
| | Localized and systemic treatment(s) | 54 (42) |

CT: Computer tomography. G1, G2, G3: Grade 1, 2 and 3. PET: Positron emission tomography. NEN: Neuroendocrine neoplasm. WHO: World Health Organization.

* Gastrointestinal collectively refers to primaries originating from: gastric, small intestine, cecum, extrahepatic biliary tract, esophagus and other.

† Localized treatment: Surgery (n=59), hepatic artery embolization (n=9), radiofrequency ablation (n=7) and/or external radiation (n=2). Systemic treatment: Interferon (n=57), somatostatin analogue (n=49), chemotherapy (n=49) and/or peptide receptor radionuclide therapy (n=43).

**TABLE 2. $^{64}$Cu-DOTATATE $SUV_{max}$ in tumor or metastases in 128 patients with neuroendocrine neoplasm**

| | | Mean (SEM) | *p-value* |
|---|---|---|---|
| Overall | | 62.2 (3.3) | - |
| Primary tumor site, grouped | | | 0.001 * |
| | Lung (*n*=7) | 63.2 (21.4) | |
| | Pancreas (*n*=25) | 83.8 (10.1) | |
| | Gastrointestinal (*n*=73) | 51.5 (2.9) | |
| | Unknown primary NEN (*n*=23) | 72.3 (7.5) | |
| WHO grade | | | 0.52 |
| | G1 (*n*=31) | 67.4 (7.5) | |
| | G2 (*n*=84) | 62.0 (3.8) | |
| | G3 (*n*=6) | 48.7 (22.7) | |
| Overall survival at 24 months | | | 0.06 |
| | Alive (*n*=99) | 65.6 (3.8) | |
| | Deceased (*n*=29) | 50.7 (5.7) | |
| Progression-free survival at 24 months | | | 0.17 |
| | No progression (*n*=62) | 66.9 (5.0) | |
| | Progression (*n*=66) | 57.8 (4.3) | |

G1, G2, G3: Grade 1, 2 and 3. NEN: Neuroendocrine neoplasm. $SUV_{max}$: Maximum Standardized Uptake Value. SEM: Standard error of mean. WHO: World Health Organization.

* Post-hoc analysis by Tukey identified $p < 0.001$ for pancreas vs. gastrointestinal $SUV_{max}$

**FIGURE 1**. Boxplot of $^{64}$Cu-DOTATATE $SUV_{max}$ by WHO Grade for 121 patients with neuroendocrine neoplasm. Abbreviations: G1, G2, G3: Grade 1, 2 and 3. $SUV_{max}$: Maximum standardized uptake value. WHO: World Health Organization.

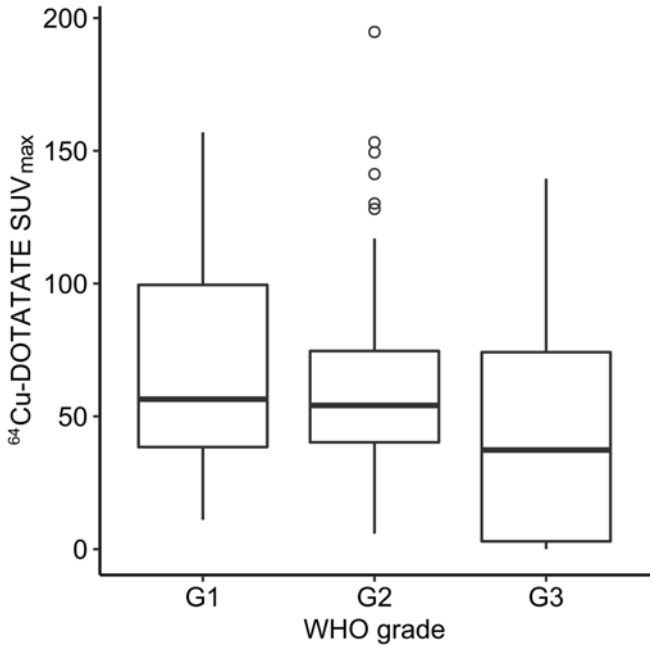


**FIGURE 2.** Kaplan-Meier plots of outcome for 128 patients with neuroendocrine neoplasms. Stratified by $^{64}$Cu-DOTATATE $SUV_{max}$ (reference: $SUV_{max} \leq 43.3$). A) Progression-free survival. B) Overall survival. Abbreviations: CI: Confidence interval. Mo: months. $SUV_{max}$: Maximum standardized uptake value.

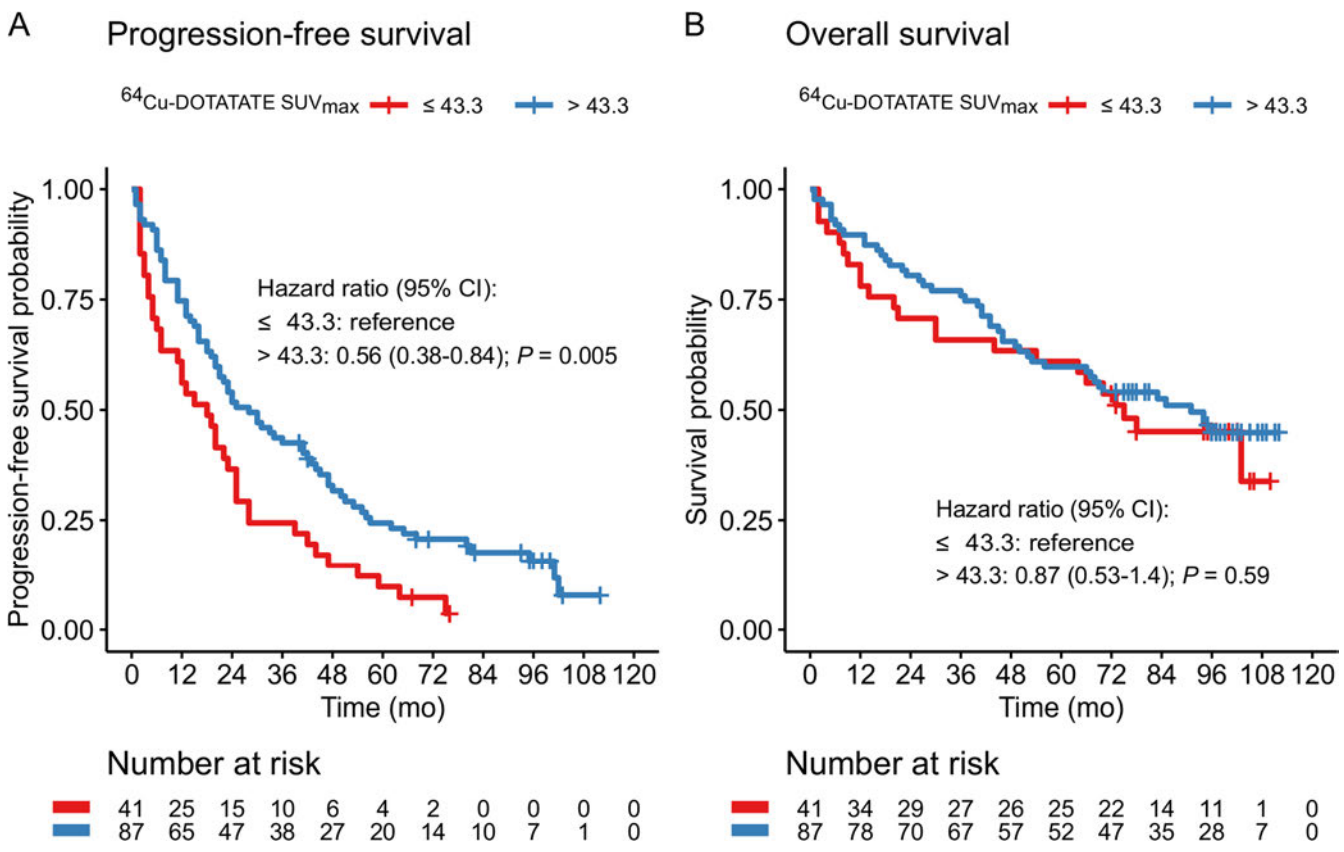


**FIGURE 3.** Plot of hazard ratios (solid line) with 95% CI (dotted lines) at several cutoffs for $^{64}$Cu-DOTATATE $SUV_{max}$. Vertical solid line at most significant cutoff A) Progression-free survival, cutoff for $SUV_{max}$: 43.3. B) Overall survival, cutoff for $SUV_{max}$: No significant cutoff identified. Abbreviations: CI: Confidence interval. HR: Hazard ratio. $SUV_{max}$: Maximum standardized uptake value.

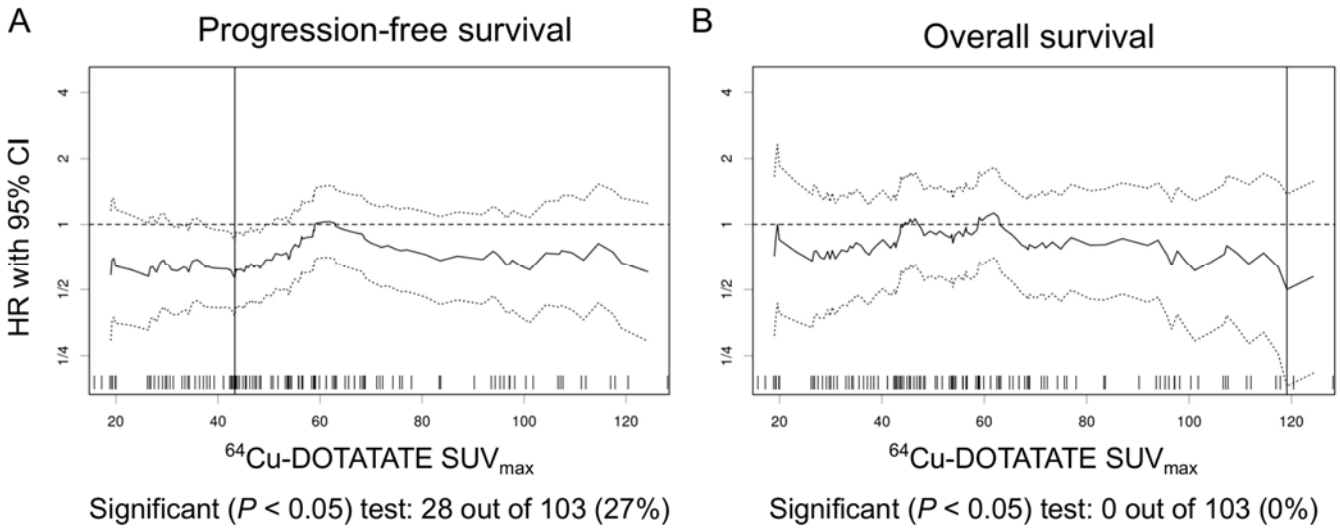


**FIGURE 4.** Kaplan-Meier plots of outcome for 121 patients with neuroendocrine neoplasms. Stratified by WHO Grade (reference: G1). A) Progression-free survival. B) Overall survival. Abbreviations: CI: Confidence interval. G1, G2, G3: Grade 1, 2 and 3. Mo: months. WHO: World Health Organization.

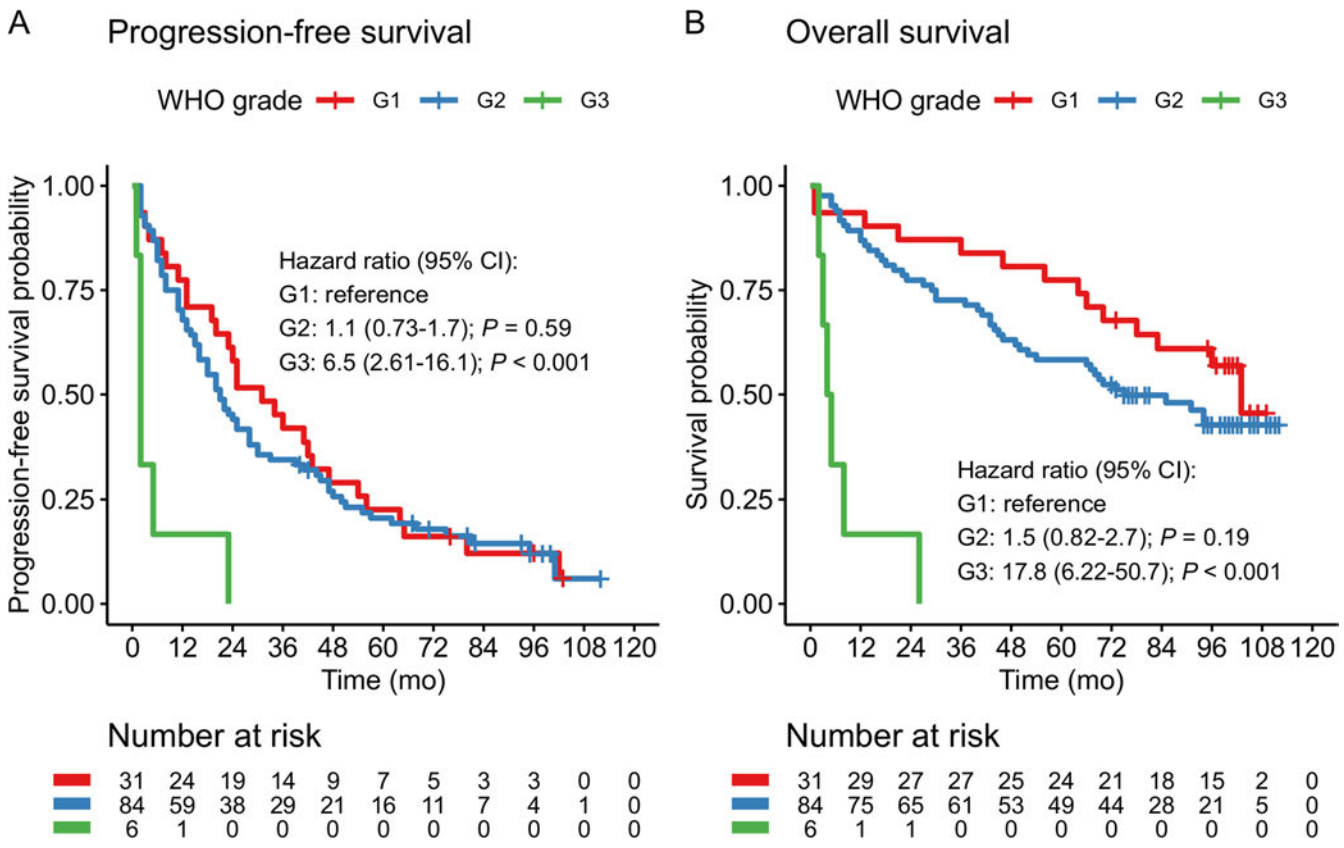
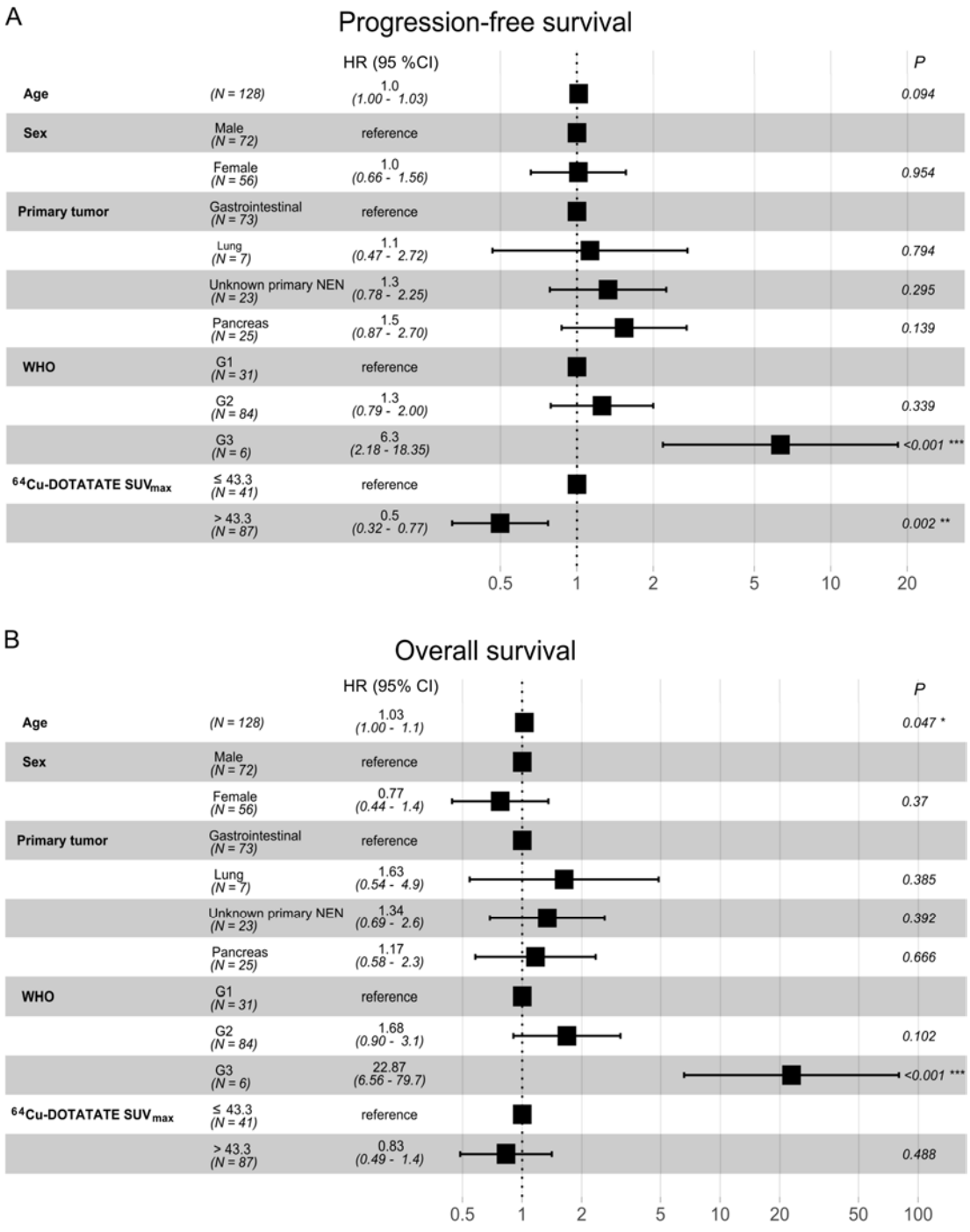


**FIGURE 5:** Forest plots of multiple Cox regression analyses to predict outcome in 128 patients with neuroendocrine neoplasms. A) Progressions-free survival. B) Overall survival. Abbreviations: CI: Confidence interval. G1, G2, G3: Grade 1, 2 and 3. HR: Hazard ratio. NEN: Neuroendocrine neoplasm. $SUV_{max}$: Maximum standardized uptake value. WHO: World Health Organization.



The Journal of NUCLEAR MEDICINE

# $^{64}$Cu-DOTATATE PET/CT and prediction of overall and progression-free survival in patients with neuroendocrine neoplasms

Esben Andreas Carlsen, Camilla Bardram Johnbeck, Tina Binderup, Mathias Loft, Andreas Pfeifer, Jann Mortensen, Peter Oturai, Annika Loft, Anne Kiil Berthelsen, Seppo W Langer, Ulrich Knigge and Andreas Kjaer

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# $^{64}$Cu-DOTATATE PET in Patients with Neuroendocrine Neoplasms: Prospective, Head-to-Head Comparison of Imaging at 1 Hour and 3 Hours Post-Injection

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## ABSTRACT

$^{64}$Cu-DOTATATE PET/CT imaging 1 hour (h) post-injection (p.i.) is excellent for lesion detection in patients with neuroendocrine neoplasms (NEN). We hypothesized that the imaging time window can be extended up to 3h p.i. without significant differences in the number of lesions detected. **Methods** From a prospective study, we compared, on a head-to-head basis, sets of $^{64}$Cu-DOTATATE PET/CT images from 35 patients with NEN scanned 1h and 3h p.i. of 200 MBq $^{64}$Cu-DOTATATE. The number of lesions on both scans were counted and grouped according to organs or regions and compared with negative binomial regression. Discordant lesions (visible on the 1h or 3h p.i. $^{64}$Cu-DOTATATE PET but not the other) were considered true if found on simultaneous CT or later MR, CT or somatostatin receptor imaging. We measured lesion maximal standardized uptake values ($SUV_{max}$), reference normal organ or tissue mean SUV ($SUV_{mean}$) and tumor-to-normal tissue ratios (TTN) calculated from $SUV_{max}$/ $SUV_{mean}$. **Results** We found 822 concordant lesions (visible on both the 1h and 3h p.i. $^{64}$Cu-DOTATATE PET) and five discordant lesions of which four were considered true. One discordant case in one patient involved a discordant organ system (lymph node) detected on the 3h p.i. but not the 1h p.i. $^{64}$Cu-DOTATATE PET that did not alter the patient's disease stage (stage IV) because the patient had 11 additional concordant liver lesions. We found no significant differences between the number of lesions detected on the 1h and 3h p.i. $^{64}$Cu-DOTATATE PET. Throughout the 1-3 h p.i. imaging window, TTN (mean [95% confidence interval]) remained high in all key organs: Liver (1h p.i.: 12.6 [10.2; 14.9] , 3h p.i.: 11.0 [8.7; 13.4]), intestines (1h p.i.: 24.2 [14.9; 33.4], 3h p.i.: 28.2 [16.5; 40.0]), pancreas (1h p.i.: 42.4 [12.3; 72.5], 3h p.i.: 41.1 [8.7; 73.4]) and bone (1h p.i.: 103.0 [38.6; 167.4], 3h p.i.: 124.2 [57.1; 191.2]). **Conclusion** The imaging time window of $^{64}$Cu-DOTATATE PET/CT of patients with NEN can be expanded from 1h p.i. to 1-3 hours p.i. without significant differences in the number of lesions detected.



**Keywords**

$^{64}$Cu-DOTATATE; Somatostatin receptor imaging; Standardized uptake values (SUV); PET/CT, Neuroendocrine neoplasms

## INTRODUCTION

Neuroendocrine neoplasms (NEN) represent a heterogeneous class of diseases with large variability in aggressiveness and prognosis. NEN most frequently originates from the pancreas, the gastro-intestinal tract or the lung (*1*). A common feature of most NEN is the overexpression of somatostatin receptors (SSTR) (*2,3*) and SSTR-imaging with radioactively labeled SSTR-specific peptides plays an important role in the staging, follow-up and treatment guidance of patients with NEN (*4-7*).

We have previously demonstrated that SSTR-targeting positron emission tomography (PET) imaging 1 hour (1h) post injection (p.i.) of 200 MBq $^{64}$Cu-DOTATATE is excellent in lesion detection in patients with NEN compared with other clinically available $^{68}$Ga-based PET and $^{111}$In-based single photon emission computed tomography (SPECT) SSTR-imaging modalities (*8,9*). Accordingly, $^{64}$Cu-DOTATATE PET was introduced at Rigshospitalet, Copenhagen, Denmark as routine SSTR-imaging of patients with NEN in 2018.

$^{64}$Cu has a low maximal positron energy (0.653 MeV) resulting in a short mean positron range (0.6 mm) that leads to excellent image resolution (*10*). For comparison, the mean positron range of $^{68}$Ga is 2.9 mm (*11*). In addition, $^{64}$Cu has the advantage of a longer half-life than $^{68}$Ga (12.7 hours vs. 68 min) that prolongs the post-synthesis usage time of $^{64}$Cu-based tracers compared with $^{68}$Ga-based tracers. This allows for central production of the tracer at a $^{64}$Cu-cyclotrone site and the tracer can then be distributed to other non-production sites with sufficient activity left at time of injection. The shelf life of $^{64}$Cu-DOTATATE is 24h (*12*) making it possible to prepare the tracer on one day and inject and image patients the following day.

The long $^{64}$Cu half-life also makes it possible to perform imaging in a broader time window and up to several hours p.i. with sufficient count statistics on later scans. An obvious benefit of the flexibility in acquisition timing is the possibility to complete a scan of an already injected patient if delays occur such that the scan cannot be completed at the target time (1h p.i.). Initial analysis from our first-in-human study with $^{64}$Cu-DOTATATE suggested that the imaging window could be extended up to at

least 3h p.i. without loss of image quality or tumor detection ability (*12*). However, the study included a relatively small number of patients and no formal quantitative analysis on the lesion numbers were performed.

The aim of the current study was therefore, on a head-to-head basis, to compare quantitatively $^{64}$Cu-DOTATATE PET/CT scans for tumor lesion detection in patients with NEN scanned at 1h p.i. and 3h p.i. in a larger group of patients. We hypothesized that the imaging time window can be expanded from 1h p.i. to 3h p.i. without significant differences in the number of lesions detected.

## MATERIALS AND METHODS

### Patients and Study Design

The study was part of our previously published prospective study of patients with NEN scanned with $^{64}$Cu-DOTATATE PET/CT at Rigshospitalet, Copenhagen, Denmark from 2009 to 2013 (*8*). In this study, the first 35 patients were $^{64}$Cu-DOTATATE PET/CT scanned both at 1h and 3h p.i. and these 35 sets of scans were included in the current head-to-head analysis. Patients were characterized by gender, age, primary tumor location, tumor functional status, tumor grade and previous NEN-related treatments. All patients had signed informed consent prior to inclusion. The study was approved by the Regional Scientific Ethical Committee (reference no. H-D-2008-045).

### Radiotracer Synthesis and Image Acquisition

$^{64}$Cu-DOTATATE production and PET/CT imaging have previously been described in detail (*8,12*). In brief, $^{64}$Cu-DOTATATE was produced in-house and the injected activity was approximately 200 MBq. Subsequent whole-body PET imaging (from scull to mid-thigh) was performed at 1h and 3h p.i. The axial *x* transaxial field of view was 216 *x* 205 mm and the acquisition time 3 minutes per bed. All patients were PET-scanned on a Biograph 64 TruePoint PET/CT scanner (Siemens Medical

Solutions) and the PET data were reconstructed with the TrueX algorithm (Siemens Medical Solutions) using 3 iterations and 21 subsets and smoothed by a Gaussian filter (2 mm full-width-half-maximum). A diagnostic CT scan was acquired prior to the 1h p.i. PET scan using a 3-mm slice thickness, 120 kV, and quality reference of 225 mA modulated by the Care Dose 4D automatic exposure control system (Siemens Medical Solutions). Unless contraindicated, patients received 75 mL of iodine-containing contrast agent administered with an automatic infusion system (Optiray 300; Covidien) with scan delays of 60 s (flow rate, 1.5 mL/s) followed by an infusion of 100 ml NaCl (flow rate, 2.5 mL/s). The diagnostic CT scan was used for attenuation correction of the 1h p.i. PET scan. Prior to the subsequent 3h p.i. PET scan, a low-dose CT (20 mA, 140 kV) without contrast was acquired for attenuation correction.

**Imaging Analysis**

The 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET/CT scans were reviewed side-by-side from June to August 2019 by the same SSTR-reader in cooperation with a radiologist blinded to the previous imaging analysis. All foci were identified on PET, and the CT was used mainly to confirm the anatomical location of the PET foci. Lesion sites were divided into organs or regions: liver, pancreas, intestines, lung/pleura, bones, lymph nodes, intra-abdominal carcinomatosis, and other (soft tissue, heart, stomach, adrenal and other less common regions) and all PET-positive lesions (defined as a clearly detectable lesion distinguishable from the surrounding tissue or organ) in each organ or region were counted. The concordance of the lesions on the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET scans was assessed for each organ or region. Discordant findings were followed up until October 2019 (up to 10 years follow up) using available MR, CT or SSTR-images to determine if the discordant finding was a true lesion. A discordant finding was considered true if the lesion had a positive CT correlate on the 1h p.i. or 3h p.i. $^{64}$Cu-DOTATATE PET/CT or could be found on a later SSRT-imaging modality or other imaging methods on follow-up.

To establish a set of reference uptake values for the $^{64}$Cu-DOTATATE PET in patients with NEN, we also quantified uptakes in lesions and normal organs and tissue on both the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET. Maximum standardized uptake values ($SUV_{max}$) of the "hottest" concordant lesion, if any, in each region or group was measured from a region of interest covering the entire lesion. Mean standardized uptake values ($SUV_{mean}$) of reference organs or tissues were measured from spherical region of interests on: a non-diseased area of the right liver lobe, the lung adjacent to the right hilus, the cauda and the uncinate process of the pancreas, spleen, intestines (ileum), the gluteal muscle and an area 5 cm below the trochanter of the right femur for bone reference. Reference values for the pituitary gland and the adrenal glands were measured with the SyngoVIA isocontur region of interest tool (default threshold of 40% of max) of a region of interest covering the entire organ. Tumor-to-normal-tissue ratios (TTN) for lesions in the liver, pancreas and lung were calculated by dividing the lesion $SUV_{max}$ with the $SUV_{mean}$ of the non-diseased area of the corresponding organ. Similarly, the femur $SUV_{mean}$ was used for bone TTN, intestinal $SUV_{mean}$ for intestinal and intra-abdominal carcinomatosis TTN, and gluteal muscle $SUV_{mean}$ for lymph node TTN. All images were analyzed using SyngoVIA Version VB30A-HF04 (Siemens Medical Solutions).

**Statistical Methods**

Differences in the number of lesions between the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET were analyzed with negative binomial regression. The 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET lesion $SUV_{max}$, reference organ and tissue $SUV_{mean}$ and TTN are shown as mean with 95 percent confidence intervals (95% CI) and were analyzed with paired T-tests adjusted for multiple comparisons by Bonferroni corrections (*13*). Two-sided p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria) version 3.6.1.

## RESULTS

### Patients and Imaging Characteristics

A total of 35 patients had 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET/CT images available and were included in the analysis. Mean [minimum, maximum] injected dose of $^{64}$Cu-DOTATATE was 205 [183, 232] MBq. Tracer uptake time was 52.9 [43, 80] min and 180.0 [167, 194] min for the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET, respectively. The characteristics of the patients are shown in Table 1.

### Lesion Numbers

The 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET showed excellent image quality with detection of the majority of the lesions on both scans. Figure 1 shows representative examples of patients with detectable lesions on both the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET/CT in different organs: liver lesions (Figure 1A), bone lesion (Figure 1B), lymph node lesion (Figure 1C) and pancreatic lesion (Figure 1D). Lesions divided into organs and regions are shown in Table 2. A total of 822 lesions (99.4 % of all lesions) were identified on both the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET (concordant lesions), while five lesions (0.6 % of all lesions) were identified on one of the PET scans, but not on the other (discordant lesions). No significant differences in the number of lesions per organ/region or in the total number of lesions were found. Table 3 shows discordant findings on a per patient basis. The five discordant lesions were detected in five different patients. In four of the cases, the discordant lesion was present on the 3h p.i. $^{64}$Cu-DOTATATE PET but not on the 1h p.i. $^{64}$Cu-DOTATATE PET. Two of the discordant lesions (patient 1: lymph node and patient 4: bone) had visible CT correlates on the $^{64}$Cu-DOTATATE PET/CT and were thus considered true positive (Figures 2 and 3). Two additional discordant findings (patients 3 and 5: liver) were considered true positive since they could be identified on later $^{68}$Ga-DOTATOC-PET (Figures 4 and 5). The remaining discordant lesion (patient 2: bone) was

considered false positive since the lesion could not be identified on later imaging modalities (Figure 6). One of the discordant lesions (patient 1: lymph node) resulted in the involvement of an additional organ system on the 3h p.i. $^{64}$Cu-DOTATATE PET not detected on the 1h p.i. $^{64}$Cu-DOTATATE PET. This patient had 11 additional concordant metastatic liver lesions.

**Quantitative Image Analysis of Lesions and Reference Organs/Tissue Uptake**

Lesion $SUV_{max}$ divided into organs/regions are shown in Table 4 and $SUV_{mean}$ of normal organs and tissues are shown in Table 5. Table 6 shows the TTN for the different lesions in patients with lesions and evaluable normal tissue in the corresponding region or organ.

**DISCUSSION**

In this prospective study of $^{64}$Cu-DOTATATE in 35 patients with NEN we investigated the hypothesis that $^{64}$Cu-DOTATATE PET may be performed from 1h to 3h p.i. without loss of the lesion detection ability compared with 1h p.i. imaging. Our main finding was that $^{64}$Cu-DOTATATE can be used for PET imaging of patients with NEN from 1-3h p.i. with high TTN (lesion contrast) and a stable lesion detection rate without significant differences in the number of lesions detected. In comparison with the fixed 1h p.i. acquisition time of $^{68}$Ga-labeled SSRT-PET tracers, the expansion of the acquisition time window of $^{64}$Cu-DOTATATE PET is convenient in the daily clinical routine.

The high agreement in the number of lesions and organ systems detected on both the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET supports the rationale of expanding the imaging time window. The two additional true positive liver lesions found on the 3h p.i. $^{64}$Cu-DOTATATE PET further suggests that in difficult cases with clinical suspicion of a small liver focus, it might be advantageous to perform late

phase $^{64}$Cu-DOTATATE PET imaging at 3h p.i. if nothing is found on the 1h p.i. $^{64}$Cu-DOTATATE PET. Of the five discordant lesions, only one case resulted in involvement of an additional organ system (patient 1: lymph node) on the 3h p.i. $^{64}$Cu-DOTATATE PET not registered on the 1h p.i. $^{64}$Cu-DOTATATE PET. Since the patient had 11 concordant metastatic liver lesions, the patient's disease stage would not have changed from stage IV as a consequence of the additional lymph node detected on the 3h p.i. $^{64}$Cu-DOTATATE PET (*14*). However, the finding of an additional extra-hepatic lesion in one patient with liver-only lesions could potentially have an impact on the clinical management. In the remaining four cases, the discordant findings involved lesions in already concordant organ systems.

The relatively short follow-up between the $^{64}$Cu-DOTATATE PET/CT and the latest available CT for patient 2 (8 months) may explain why the discordant bone lesion could not be confirmed. For $^{64}$Cu-DOTATATE (*8,9*), $^{68}$Ga-DOTATOC (*15*) and $^{68}$Ga-DOTATATE (*16*), bone lesions are detected on PET several months to years prior to detection on CT in some cases. Alternatively, the finding may represent an artifact on the 1h p.i. $^{64}$Cu-DOTATATE PET. Importantly, the patient also had several concordant bone lesions. The clinical consequences of the false positive findings are very limited.

It has been questioned whether the $^{64}$Cu-DOTATATE liver uptake could be a challenge for detection of liver lesions. Although a numerical increase in the mean liver $SUV_{mean}$ on the 3h p.i. compared with the 1h p.i. $^{64}$Cu-DOTATATE PET was seen, the median liver $SUV_{mean}$ for $^{64}$Cu-DOTATATE in our study (1h p.i. 3.86 and 3h p.i. 5.52) was still lower at both time points compared to what has been reported for another $^{64}$Cu-labeled SSTR-PET tracer $^{64}$Cu-SARTATE (1h p.i. 7.10 and 4h p.i. 5.90) (*17*). The mean liver $SUV_{mean}$ at both 1h p.i. and 3h p.i. for $^{64}$Cu-DOTATATE was also within the range or lower than that reported for $^{68}$Ga-DOTATATE at 1h p.i.: 4.5 (*18*) to 7.2 (*19*). In addition, because the liver lesion $SUV_{max}$ also increased from the 1h p.i. to 3h p.i. $^{64}$Cu-DOTATATE, the mean liver TTN remained high and almost unchanged from 1h p.i. to 3h p.i. (12.6 vs 11.0). Importantly, moreover the liver lesion detection ability at 3h p.i. was not affected as two additional true liver lesions were identified on

the 3h p.i. $^{64}$Cu-DOTATATE PET. Although it could be discussed whether the use of two different CT scans for the attenuation correction for the 1h p.i. and 3h p.i. PET could have contributed to differences in the quantification at the two time points, we find this unlikely to have been of any clinical relevance (*20,21*).

It could be speculated whether differences in liver background and liver lesion uptake between the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET should be taken into consideration when $^{64}$Cu-DOTATATE PET is used for selection of patients for peptide receptor radionuclide therapy (PRRT). However, apart from a single bone lesion, all lesions in all the patients were above liver background uptake both at 1h p.i. and 3h p.i.. Therefore, if the a modified Krenning scale had been applied, the conclusions would be similar whether based on 1h p.i. or 3h p.i. $^{64}$Cu-DOTATATE PET. However, if more quantitative cut-offs will be established in the future for guiding PRRT, they are likely to be both PET tracer and scan time specific.

The high TTNs measured on both the 1h p.i. to 3h p.i. $^{64}$Cu-DOTATATE PET throughout the different organs and regions suggest that the tumor delineation from the surroundings remains sufficient in the 1-3h p.i. time window. Combined with the high concordance in the number of lesions detected on both the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET, this observation supports the conclusion that no clinically relevant loss in image information occurs within the 1-3h p.i. imaging window.

## CONCLUSION

$^{64}$Cu-DOTATATE PET/CT has excellent performance from 1-3h p.i. for imaging patients with NEN without significant differences in the number of lesions detected. The maintained lesion detection rate and high contrast from 1-3h p.i., combined with the shelf life of 24h, adds to the convenience and flexibility of using $^{64}$Cu-DOTATATE PET for routine imaging of patients with NEN.

## KEYPOINTS

**QUESTIONS:** Can the imaging time window for $^{64}$Cu-DOTATATE PET be expanded from 1 hour post-injection (p.i.) to 1-3 hours p.i. in patients with neuroendocrine neoplasms (NEN)?

**PERTINENT FINDINGS:** $^{64}$Cu-DOTATATE PET/CT imaging has excellent performance with high TTN and conserved lesion detection ability from 1-3 hours p.i. in patients with NEN.

**IMPLICATIONS FOR PATIENT CARE:** The imaging time window can be expanded from 1 hour p.i. to 1-3 hours p.i. which adds to the convenience and flexibility of using $^{64}$Cu-DOTATATE PET for routine imaging in patients with NEN.

## DISCLOSURE

Andreas Kjaer and Ulrich Knigge are inventors on patent/applications covering “PET tracer for imaging of neuroendocrine tumors”. The other authors have no potential conflicts of interests relevant to this article.

## ACKNOWLEDGEMENTS

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**FIGURE 1** Representative examples of lesions in the same patients scanned at 1h p.i. and 3h p.i. From left to right: CT, $^{64}$Cu-DOTATATE PET, fused $^{64}$Cu-DOTATATE PET/CT and maximum intensity projection (MIP) with corresponding SUV color bars below. For each example, the 1h p.i. $^{64}$Cu-DOTATATE PET/CT is on top and the 3h p.i. $^{64}$Cu-DOTATATE PET/CT in on the bottom. **A** Liver lesions, **B** bone lesion, **C** lymph node lesion, **D** pancreatic lesion. All lesions were identified on both the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET. Ant: anterior, Post: posterior, R: right, L: left, H: head, F: feet.

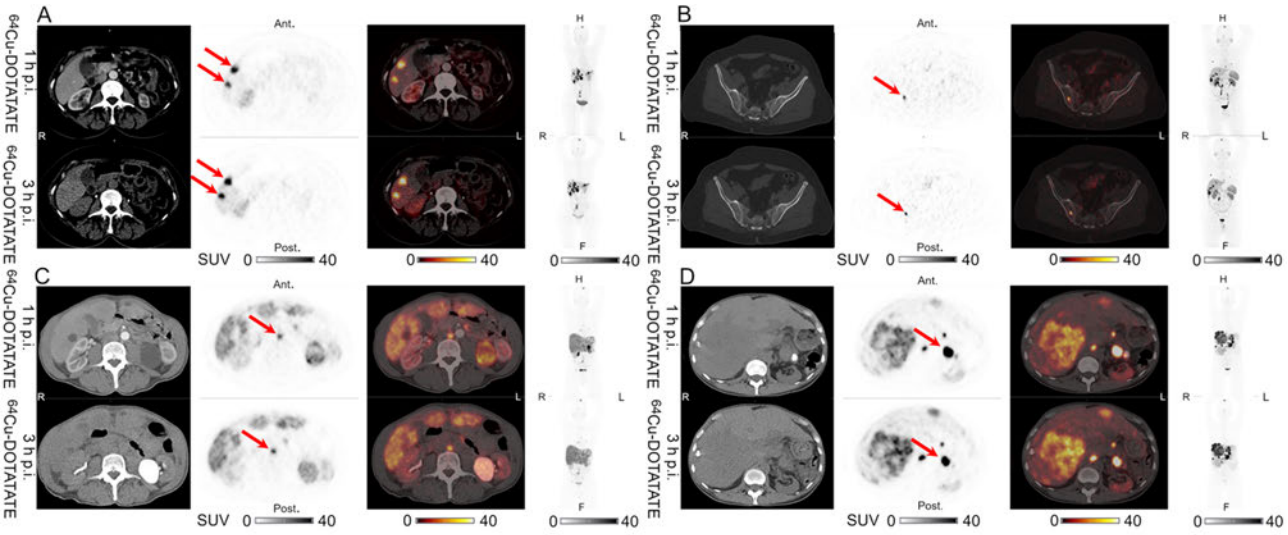

**FIGURE 2** Patient 1: One additional lymph node lesion visible on 3h p.i. $^{64}$Cu-DOTATATE PET (middle) but not 1h p.i. $^{64}$Cu-DOTATATE PET (top) with visible CT correlate. The lymph node lesion was also visible on later 1h p.i. $^{64}$Cu-DOTATATE-PET/CT with CT correlate performed 9 months after the initial scan (bottom). True positive. From left to right: CT, $^{64}$Cu-DOTATATE PET, fused $^{64}$Cu-DOTATATE PET/CT and MIP with corresponding SUV color bars below. Ant.: anterior, Post.: posterior, R: right, L: left, H: head, F: feet.

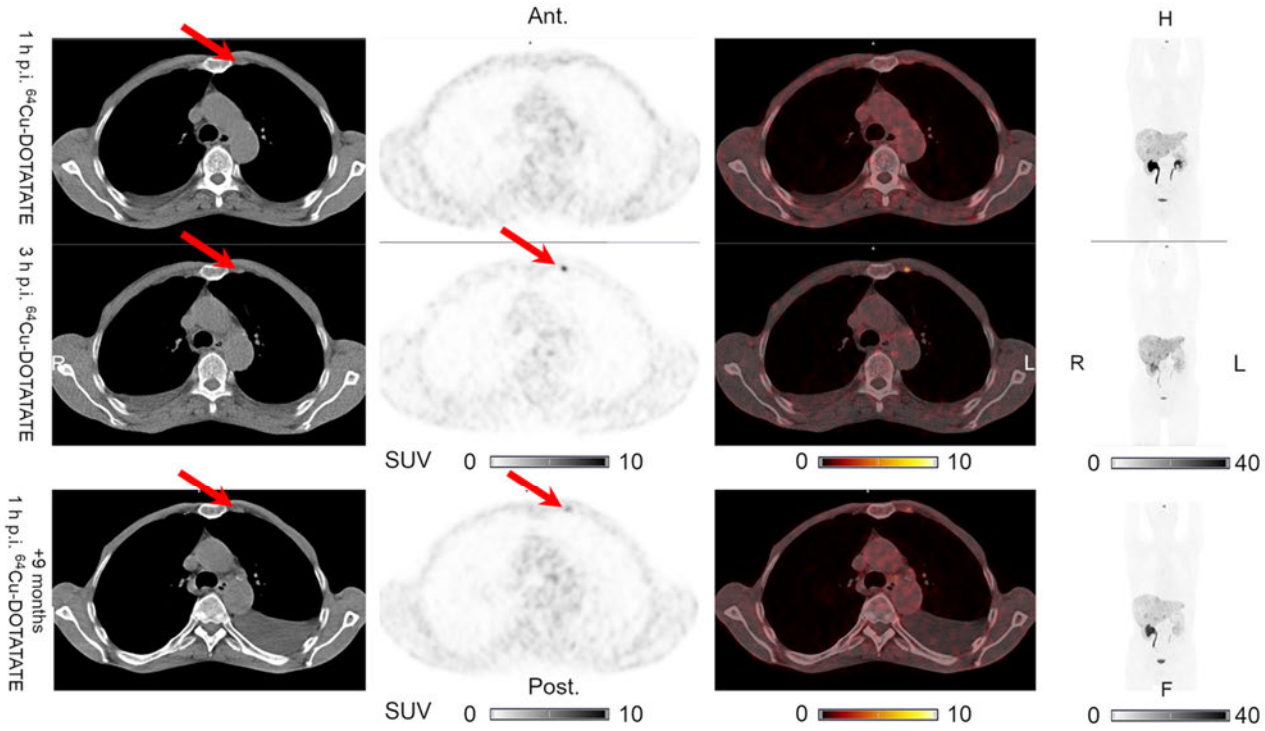

**FIGURE 3** Patient 4: One additional bone lesion visible on 3h p.i. $^{64}$Cu-DOTATATE-PET (bottom) but not 1h p.i. $^{64}$Cu-DOTATATE PET (top) with visible CT correlate. True positive. No later SSTR-PET available. From left to right: CT, $^{64}$Cu-DOTATATE PET, fused $^{64}$Cu-DOTATATE PET/CT and MIP with corresponding SUV color bar below. A: anterior, P: posterior, R: right, L: left, H: head, F: feet.

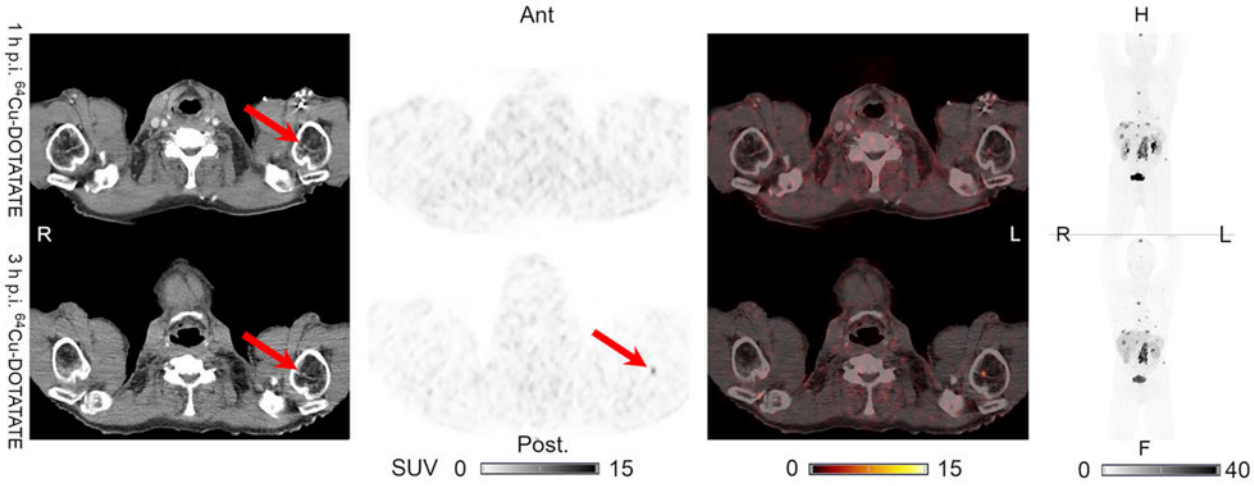

**FIGURE 4** Patient 3: One additional liver lesion visible on 3h p.i. $^{64}$Cu-DOTATATE PET (middle) but not on 1h p.i. $^{64}$Cu-DOTATATE PET (top) without CT correlate. Discordant liver lesion visible on later 1h p.i. $^{68}$Ga-DOTATOC-PET (46 months after the scan) with visible CT correlate (bottom). True positive. From left to right: CT, PET, fused PET/CT and MIP with corresponding SUV color bars below. Ant.: anterior, Post.: posterior, R: right, L: left, H: head, F: feet.

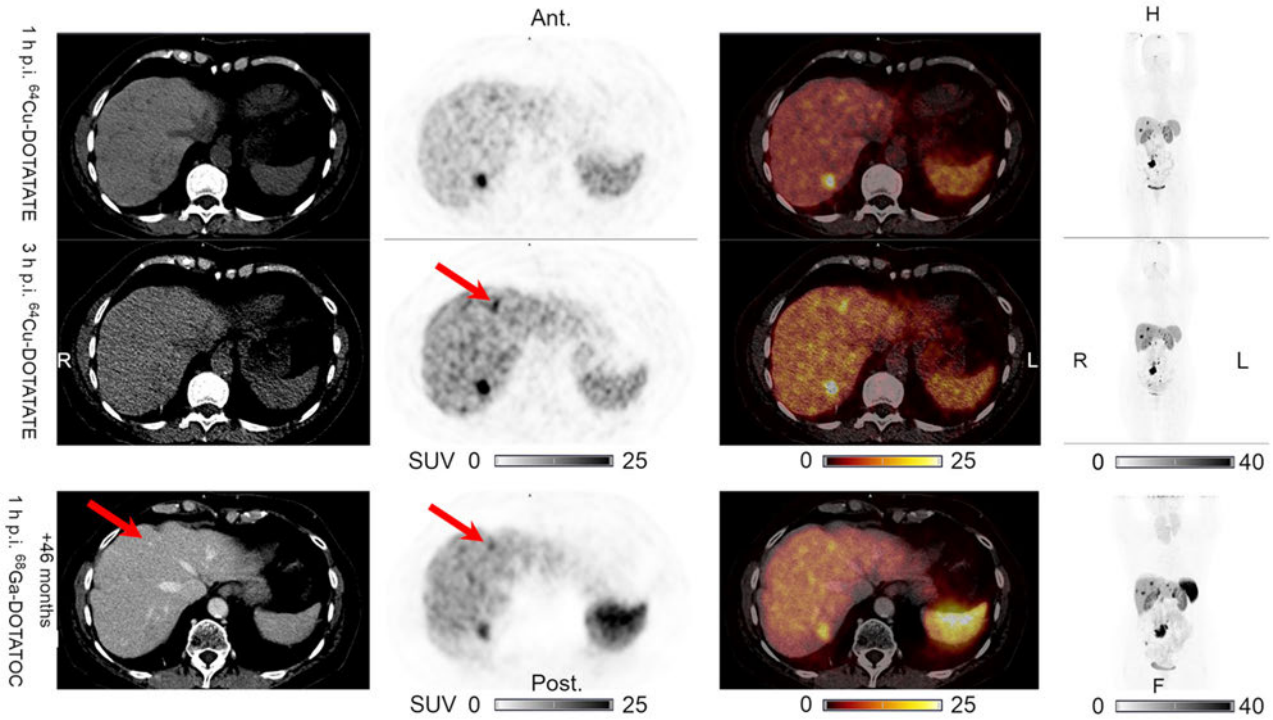

**FIGURE 5** Patient 5: One additional liver lesion visible on 3h p.i. $^{64}$Cu-DOTATATE PET (middle) but not on 1h p.i. $^{64}$Cu-DOTATATE PET (top). No visible CT correlate. Discordant liver lesion visible on later 1h $^{68}$Ga-DOTATOC-PET/CT (39 months after the scan) without visible CT correlate (bottom). True positive. From left to right: CT, PET, fused PET/CT and MIP with corresponding SUV color bars below. Ant: anterior, Post: posterior, R: right, L: left, H: head, F: feet.

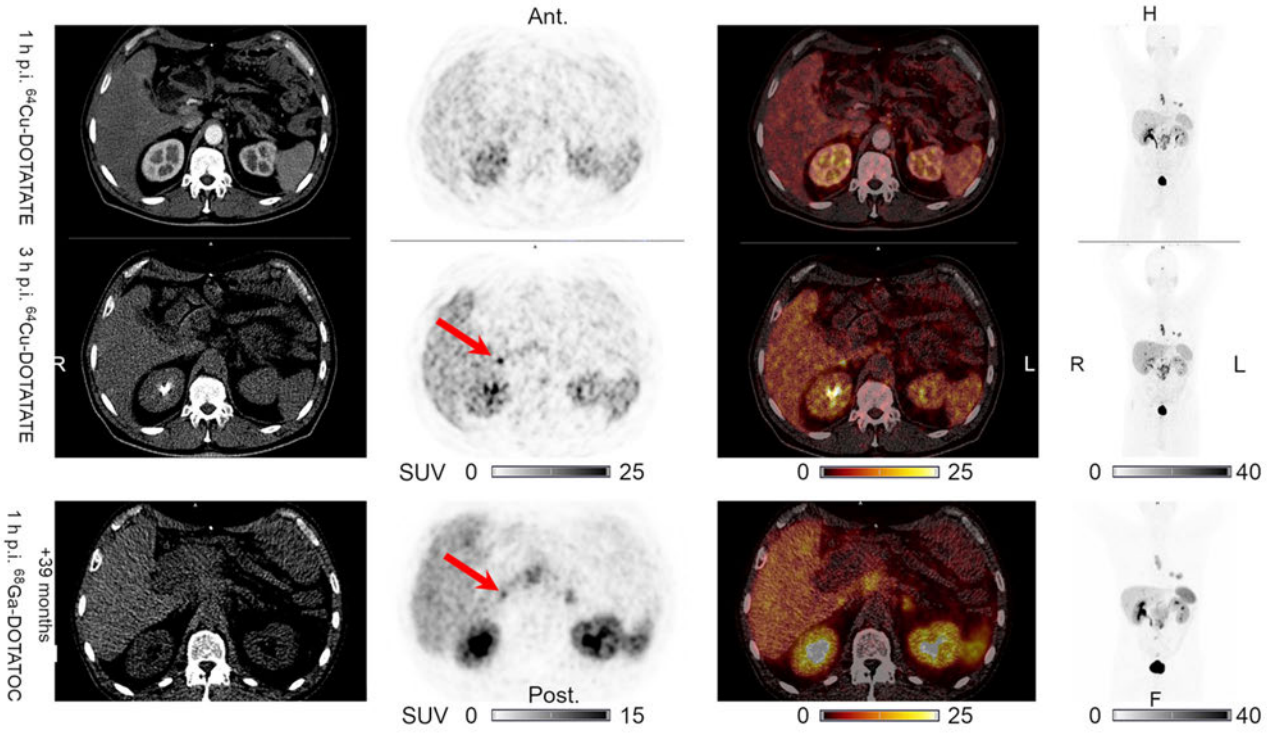

**FIGURE 6** Patient 2: One additional bone lesion visible on the 1h p.i. $^{64}$Cu-DOTATATE PET (top) but not 3h p.i. $^{64}$Cu-DOTATATE PET without CT correlate (bottom). No later SSTR-PET available. No visible CT correlate on the latest CT-scan (8 months after the $^{64}$Cu-DOTATATE PET/CT). False positive. From left to right: CT, $^{64}$Cu-DOTATATE PET, fused $^{64}$Cu-DOTATATE PET/CT and MIP with corresponding SUV color bars below. A: anterior, P: posterior, R: right, L: left, H: head, F: feet.

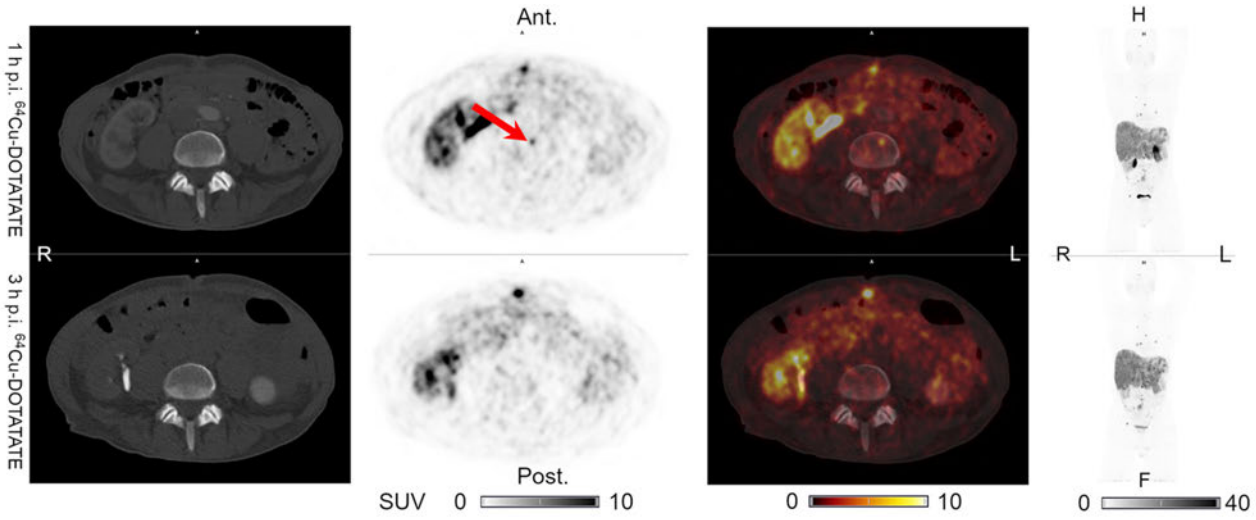

**TABLE 1 Characteristics of 35 patients with neuroendocrine neoplasms examined on 1h and 3h p.i. $^{64}$Cu-DOTATATE PET/CT.**

| | Total: 35 patients |
|---|---|
| **Gender n (%)** | |
| Male | 21 (60%) |
| Female | 14 (40 %) |
| **Age** | |
| Mean [minimum, maximum] | 62 [40, 81] |
| **Site of Primary Tumor n (%)** | |
| Lung | 3 (9%) |
| Gastrointestinal | 13 (37%) |
| Pancreatic | 5 (14%) |
| Other | 2 (6%) |
| Unknown | 12 (34%) |
| **Functional Status n (%)** | |
| Non-functioning | 20 (57%) |
| Functioning (carcinoid syndrome) | 15 (43%) |
| **Grade n (%)** | |
| Low-grade (G1) | 8 (23%) |
| Intermediate grade (G2) | 21 (60%) |
| High grade (G3) | 2 (6%) |
| KI-67 proliferation index not available | 4 (11%) |
| **Primary Tumor Removed n (%)** | |
| No | 20 (57%) |
| Yes | 15 (43%) |
| **Previous treatments* n (%)** | |
| Surgery | 15 (43%) |
| Interferon α | 19 (54%) |
| Somatostatin analogues | 14 (40%) |
| Radio frequency Ablation (liver metastases) | 3 (9%) |
| External radiation therapy | 1 (3%) |
| Peptide receptor radionuclide therapy (PRRT) | 12 (34%) |

*Some patients received multiple treatments. Therefore, the total number of treatments exceeded the number of patients.

**TABLE 2 Comparison of lesions per organ or region in 35 patients with neuroendocrine neoplasms**

| Organ/region | Concordant lesions | Only on 1h p.i. $^{64}$Cu-DOTATATE PET | Only on 3h p.i. $^{64}$Cu-DOTATATE PET | P† |
|---|---|---|---|---|
| Lung | 14 | 0 | 0 | - |
| Liver | 298 | 0 | 2 | 0.98 |
| Intestines | 18 | 0 | 0 | - |
| Pancreas | 12 | 0 | 0 | - |
| Intra-abdominal Carcinomatosis | 7 | 0 | 0 | - |
| Bone | 326 | 1 | 1 | 1.00 |
| Lymph nodes | 114 | 0 | 1 | 0.98 |
| Other* | 33 | 0 | 0 | - |
| Total | 822 | 1 | 4 | 0.99 |

*Other locations: 22 soft tissue lesions, 5 heart lesions, 1 prostate, 1 adrenal, 1 stomach, 1 thyroid, 1 brain and 1 spleen lesion. †P values for tests for differences in the number of lesions with negative binominal regression per organ or region, and the total number of lesions between the 1h p.i. and 3h p.i. $^{64}$Cu-DOTATATE PET.

**TABLE 3 Discordant lesions per patient comparison in 35 patients with neuroendocrine neoplasms**

| ID | Concordant | Only on 1h p.i. $^{64}$Cu-DOTATATE | Only on 3h p.i. $^{64}$Cu-DOTATATE | Status | Months until follow-up | Modality | Discordant organ system |
|---|---|---|---|---|---|---|---|
| 1 | Liver (11) | | LN (1) | TP | 0*/9 | CT/Cu | LN |
| 2 | Bone (15), LN (7), Lung (1), Carc (1), Liver (43) | Bone (1) | | FP | 8 | CT | None |
| 3 | Liver (6), LN (8), Int (1) | | Liver (1) | TP | 46/46 | Ga/CT | None |
| 4 | Bone (19), Spleen (1), Int (1), Adre (1), Heart (3), Liver (5) | | Bone (1) | TP | 0* | CT | None |
| 5 | Liver (2), LN (19) Heart (2), Int (1) | | Liver (1) | TP | 39 | Ga | None |

*Visible CT correlate on the $^{64}$Cu-DOTATATE PET/CT. LN = Lymph nodes, Carc = intra-abdominal carcinomatosis, Adre = adrenal, Int = intestines, TP=true positive, FP = false positive, Ga = $^{68}$Ga-DOTATOC PET, Cu = 1h p.i. $^{64}$Cu-DOTATATE PET (follow-up scan).

**TABLE 4 Lesion $SUV_{max}$ in 35 patients with neuroendocrine neoplasms**

| | | Lesion $SUV_{max}$† | | |
|---|---|---|---|---|
| **Organ / region** | **n*** | **1h p.i. $^{64}$Cu-DOTATATE** | **3h p.i. $^{64}$Cu-DOTATATE** | **P§** |
| Lung | 5 | 17.9 [3.0; 32.9] | 18.7 [5.3; 32.1] | 1.00 |
| Liver | 22 | 45.7 [37.2; 54.3] | 54.1 [44.3; 64.0] | <0.01 |
| Intestines | 12 | 64.4 [43.9; 84.8] | 77.8 [52.3; 103.3] | 0.19 |
| Pancreas | 8 | 79.0 [38.3; 119.6] | 85.9 [35.9; 135.8] | 1.00 |
| Bone | 12 | 44.2 [25.7; 62.7] | 50.1 [29.7; 70.4] | 0.46 |
| Intra-abdominal carcinomatosis | 4 | 23.0 [7.7; 38.3] | 24.9 [9.0; 40.7] | 1.00 |
| Lymph nodes | 18‡ | 40.9 [26.9; 54.9] | 43.5 [29.1; 58.0] | 0.76 |

*Number of patients with lesions. †Mean [95% CI]. ‡One additional lymph node lesion detected in one patient on the 3h p.i. $^{64}$Cu-DOTATATE PET (n=19 on 3h p.i. PET). §P-values for paired T-tests adjusted for multiple comparisons with Bonferroni correction (N=7) and capped at 1.00.

**TABLE 5 Normal tissue and organ $SUV_{mean}$ in 35 patients with neuroendocrine neoplasms**

| | | Normal organ or tissue $SUV_{mean}$† | | |
|---|---|---|---|---|
| **Organ / region** | **n*** | **1h p.i. $^{64}$Cu-DOTATATE** | **3h p.i. $^{64}$Cu-DOTATATE** | **P‡** |
| Lung | 35 | 0.27 [0.23; 0.30] | 0.15 [0.13; 0.17] | <0.01 |
| Liver | 32 | 4.0 [3.6; 4.4] | 5.7 [5.2; 6.3] | <0.01 |
| Intestines | 35 | 2.6 [2.1; 3.1] | 2.5 [2.0; 3.1] | 1.00 |
| Uncinate process of pancreas | 31 | 3.2 [2.7; 3.6] | 3.3 [2.7; 3.9] | 1.00 |
| Cauda of pancreas | 32 | 3.1 [2.8: 3.5] | 3.5 [3.2; 3.9] | 0.38 |
| Bone | 35 | 0.76 [0.66; 0.85] | 0.64 [0.56; 0.73] | <0.01 |
| Muscle | 35 | 0.63 [0.57; 0.69] | 0.49 [0.44; 0.54] | <0.01 |
| Spleen | 35 | 8.9 [7.8; 10.0] | 9.3 [8.2; 10.4] | 0.12 |
| Pituitary gland | 35 | 12.9 [10.8; 14.9] | 15.8 [13.4; 18.2] | <0.01 |
| Adrenal gland | 33 | 9.5 [8.0; 11.0] | 9.9 [8.2; 11.6] | 1.00 |

*Number of patients with evaluable normal organ or tissue. †Mean [95% CI]. ‡P-values for paired T-tests adjusted for multiple comparisons with Bonferroni correction (N=10) and capped at 1.00.

**TABLE 6 Tumor to normal tissue/organ ratios (TTN) in 35 patients with neuroendocrine neoplasms**

| | | TTN† | | |
|---|---|---|---|---|
| **Organ / region** | **n*** | **1h p.i. $^{64}$Cu-DOTATATE** | **3h p.i. $^{64}$Cu-DOTATATE** | **P§** |
| Lung | 5 | 87.9 [30.2; 145.6] | 160.9 [79.2; 242.6] | 0.04 |
| Liver | 19 | 12.6 [10.2; 14.9] | 11.0 [8.7; 13.4] | 0.03 |
| Intestines | 12 | 24.2 [14.9; 33.4] | 28.2 [16.5; 40.0] | 0.73 |
| Pancreas | 6 | 42.4 [12.3; 72.5] | 41.1 [8.7; 73.4] | 1.00 |
| Bone | 12 | 103.0 [38.6; 167.4] | 124.2 [57.1; 191.2] | 0.07 |
| Intra-abdominal Carcinomatosis | 4 | 14.0 [3.0; 25.0] | 22.5 [7.1; 38.0] | 0.50 |
| Lymph nodes | 18‡ | 73.7 [43.0; 104.4] | 94.0 [61.6; 126.4] | 0.07 |

*Number of patients with lesions and evaluable normal tissue. †Mean [95% CI]. ‡One additional lymph node lesion detected in one patient on 3h p.i. $^{64}$Cu-DOTATATE PET (n=19 on 3h p.i. PET). §P-values for paired T-tests adjusted for multiple comparisons with Bonferroni correction (N=7) and capped at 1.00.

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# $^{64}$Cu-DOTATATE PET in Patients with Neuroendocrine Neoplasms: Prospective, Head-to-Head Comparison of Imaging at 1 Hour and 3 Hours Post-Injection

Mathias Loft, Esben Andreas Carlsen, Camilla Bardram Johnbeck, Helle Hjorth Johannesen, Tina Binderup, Andreas Pfeifer, Jann Mortensen, Peter Oturai, Annika Loft, Anne Kiil Berthelsen, Seppo Wang Langer, Ulrich Knigge and Andreas Kjaer

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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 U.S. Prospective, Reader-Masked Clinical Trial

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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 on 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 masked to all clinical information read PET/CT scans from 21 healthy volunteers and 42 NET-positive patients to determine those with disease or no disease, as well as those with localized versus metastatic status. Masked-reader evaluations were compared with a patient-specific standard of truth, 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 intrareader reliability, as well as ability to differentiate between localized and metastatic disease, was also determined. Adverse events were recorded from $^{64}$Cu-DOTATATE injection through 48 h after injection. **Results:** The dose-ranging study identified 148 MBq (4.0 mCi) as the optimal dose to obtain diagnostic-quality PET/CT images. After 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 standard-of-truth misread. Excellent inter- and intrareader reliability, as well as ability to distinguish between localized and metastatic disease, was also noted. No adverse events were related to $^{64}$Cu-DOTATATE, and no serious adverse events 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

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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 diethylenetriaminepentaacetic acid (DTPA) octreotide (OctreoScan; Mallinckrodt) in the mid 1990s significantly improved the accuracy with which patients with NETs were identified, staged, and monitored. Octreotide is a somatostatin analog that binds specifically to SSTR types 2 and 5 and allows the molecular imaging and characterization of NETs (*2,3*). After determining SSTR positivity with $^{111}$In DTPA octreotide SPECT, peptide receptor radionuclide therapy could then be instituted using therapeutic radionuclides (e.g., $^{177}$Lu and $^{90}$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 U.S. Food and Drug Administration approved the radiopharmaceutical $^{68}$Ga DOTATATE to be used with PET, an imaging modality with higher resolution than SPECT (*3*). Additionally, the higher affinity of DOTATATE than of 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

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somatostatin analog PET radiotracer that has demonstrated lower radiation dose and higher lesion detection rates than $^{111}$In DTPA octreotide, as well as a lesion detection rate superior to that of $^{68}$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 at tractive for routine clinical imaging (*2,7*).

The primary objective of this first U.S. phase III, prospective, reader masked, controlled pivotal trial was to assess the sensitivity and specificity of $^{64}$Cu DOTATATE PET/CT imaging for detecting NETs in subjects with or without disease against a standard of truth (SOT) for each subject. However, unlike most diagnostic perfor mance studies, the phase III study was preceded by an independent dose ranging study to determine the optimal dose for obtaining di agnostic quality PET/CT images. Secondary objectives were to com pare 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 with the SOT, and assess inter and intrareader 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 3 $^{64}$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 ac quired at 60 ± 15 min after injection and with a 5 min acquisition time per bed position. Image quality was evaluated by 3 experienced readers masked 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 de lineation is suboptimal and small lesions [1 cm] are hard to assess); and 2, acceptable (clear images; large and small lesion delineation is possible). Cohort scores were calculated by adding together the aver age 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 of at least 7 was deemed the lowest

**TABLE 1**
Demographics and Baseline Characteristics (Safety Population)

| Characteristic | Dose-ranging study (*n* 12) | Phase III study (*n* 63) |
|---|---|---|
| Age (y) | | |
| Mean | 62.0 (12.7) | 54.4 (15.7) |
| Median | 59.5 (44.0, 83.0) | 54.0 (25.0, 82.0) |
| Height (cm) | | |
| Mean | 172.1 (9.9) | 171.9 (11.43) |
| Median | 171.4 (157.4, 193.0) | 172.7 (147.3, 199.9) |
| Weight (kg) | | |
| Mean | 72.4 (19.8) | 84.3 (21.2) |
| Median | 69.8 (45.3, 113.4) | 80.7 (51.7, 148.3) |
| Sex | | |
| Male | 5 (41.7) | 28 (44.4) |
| Female | 7 (58.3) | 35 (55.6) |
| Race | | |
| 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 | | |
| 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) |

Qualitative data are numbers followed by percentages in parentheses; continuous data are mean followed by SD and median followed by range in parentheses.

$^{64}$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, 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 masked to the SOT. Patient demographics and characteristics are shown in Table 1. To obtain at least a 90% chance of showing more than 0.70 sensitivity and more than 0.60 specificity, 63 subjects were required. After a preestablished 2:1 (NET positive/NET negative) ratio, 42 SOT positive patients and 21 SOT negative healthy volunteers were recruited under a U.S. 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 MRI, CT, $^{18}$F FDG 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 Biomedical Research Alliance of New York Institutional Review Board, 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, and DOTATATE peptide was manufactured by ABX GmbH. $^{64}$Cu DOTATATE drug was prepared by RadioMedix, Inc., according to current good manufacturing practice guidelines. Briefly, $^{64}CuCl_2$ (5,550 9,250 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 min at 95°C and then passed through a Sep Pak C18 cartridge (Waters). 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 more than 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 Biograph Horizon 16 slice scanner (Siemens Healthineers). PET/CT scans were undertaken on average 63 min (median, 60 min; range, 39 97 min) after a single intravenous dose of 148 MBq ± 10% (range, 132 163 MBq) of $^{64}$Cu DOTATATE. PET scans (from vertex of skull to mid thigh) were obtained in 3 dimensional mode, with an acquisition time of 5 min per bed position over an approximately 30 min total scan time. A noncontrast 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 research contract organization that masked all clinical, imaging, and laboratory information. Thereafter, the contract organization randomized the images to 3 experienced, independent, board certified nuclear medicine physicians who had been trained previously by the contract organization to detect abnormal images associated with SSTRs. Readers 1, 2, and 3 had 37, 5, and 8 y of experience in nuclear medicine, respectively, and all had read hundreds of $^{68}$Ga based SSTR PET/CT scans. On 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 subcategorized as localized or metastatic, as appropriate. Ten percent of the images (7 cases) were randomly selected for assessment of interreader variability by reintroducing the images to the independent readers for a second masked read no earlier than 4 wk 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 as localized or metastatic, as appropriate.

### Safety Assessments

Safety was determined primarily through investigator assessed treatment emergent adverse events. An adverse event was considered treatment emergent if the start date and time were 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 h after injection 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 h before and 2 h after $^{64}$Cu DOTATATE administration. The 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 indicate a mild adverse event, a moderate adverse event, a severe or medically significant but not life threatening adverse event, a life threatening adverse event, and death related to an adverse event, respectively.

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

For 8 subjects of child bearing potential, a urine pregnancy test was performed before 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 the Wilson score with continuity correction (the score method). The level of significance for each hypothesis test was a 1 sided $\alpha$ value of 0.025. Point estimates of sensitivity and specificity were calculated along with 2 sided 95% confidence intervals using the score method. Sensitivity and specificity were calculated on an individual reader basis. In addition, a majority read statistical analysis 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 on the primary endpoints could be declared if 2 of the 3 independent readers achieved a sensitivity and a specificity exceeding preestablished thresholds.

Analysis of NPV, PPV, and accuracy was computed using the majority read (i.e., the majority $^{64}$Cu DOTATATE diagnosis from the 3 readers) and using reader reports. Point estimates of the majority read and individual reader NPV, PPV, and accuracy were calculated

**TABLE 2**
Image Scoring of 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, and large and small lesion delineation is possible).

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

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 (i.e., sensitivity and specificity). Thus, *P* values were calculated for sensitivity and specificity and not for PPV, NPV, or accuracy. *P* values of less than 0.05 were considered statistically significant.

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

The data analyses were conducted using SAS Software, version 9.4 or higher (IBM).

## RESULTS

### Dose-Ranging Study

Table 2 shows the image scoring of the 3 masked 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 image quality superior to that of the 111 MBq (3.0 mCi) dose. On the basis of 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 had 90.9% ($P = 0.0042$) and 80.0% ($P = 0.0172$), respectively; and reader 3 had 90.9% ($P = 0.0042$) and 90.0% ($P = 0.0003$), respectively. 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 of at least 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 1 sided α value of 0.025.

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

**TABLE 3**
Individual Reader and Majority Reads for $^{64}$Cu-DOTATATE PET/CT Imaging Versus SOT

| Parameter | 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) |

*Statistical analysis plan included testable hypothesis for coprimary endpoints (i.e., sensitivity and specificity). Thus, *P* values were calculated for sensitivity and specificity and not for PPV, NPV, or accuracy.

Confidence intervals are in parentheses, and *P* values are in brackets ($P < 0.05$ is considered statistically significant).

of NET negative (no disease) by the oncologist who established the SOT. Because the objective of the study was to assess not the SOT oncologist's read but 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 because of 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 sensitivity, specificity, PPV, NPV, and accuracy for the per patient majority read were 100.0% ($P = 0.0002$), 96.8% ($P < 0.0001$), 96.7%, 100.0%, and 98.4%, respectively. Further, the ability to differentiate between metastatic and localized disease with $^{64}$Cu DOTATATE PET/CT revealed a majority read with 100.0% sensitivity and 100.0% specificity.

### Inter- and Intrareader Agreement (Tertiary Objectives)

Overall, the 3 readers demonstrated a substantial degree of interreader 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 interreader agreement for assessment of $^{64}$Cu DOTATATE PET/CT imaging.

For the intrareader variability, readers 1 and 3 demonstrated perfect intrareader agreement on the image reread ($\kappa = 1.0000$). Table 5 summarizes intrareader agreement for $^{64}$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 min after injection or at discharge) occurred. Additionally, no changes were observed in electrocardiogram parameters from baseline to 1 h after injection of $^{64}$Cu DOTATATE.

**TABLE 4**
Summary of Interreader Agreement for Assessment of $^{64}$Cu-DOTATATE PET/CT Imaging

| Reader pair | *n* | κ | 95% CI on κ |
|---|---|---|---|
| 1 vs. 2 | 62* | 0.7419 (SE, 0.0844) | 0.5764, 0.9074 |
| 1 vs. 3 | 62* | 0.8710 (SE, 0.0623) | 0.7489, 0.9930 |
| 2 vs. 3 | 63 | 0.7123 (SE, 0.0883) | 0.5392, 0.8855 |
| Overall | 63 | 0.7664 (SE, 0.0732) | 0.6229, 0.9099 |

*Reader 1 could not evaluate $^{64}$Cu-DOTATATE PET/CT of 1 subject because of image artifact caused by breathing motion.
CI confidence interval.

**TABLE 5**
Intrareader Agreement of $^{64}$Cu-DOTATATE PET/CT Imaging

| Reader | Parameter | Estimate | 95% CI |
|---|---|---|---|
| 1 | κ | 1.0000 | 1.0000, 1.0000 |
| | Uncorrected agreement | 1.0000 | 0.5904, 1.0000 |
| 2 | κ | 0.5333 | 0.0596, 1.0000 |
| | Uncorrected agreement | 0.7143 | 0.2904, 0.9633 |
| 3 | κ | 1.0000 | 1.0000, 1.0000 |
| | Uncorrected agreement | 1.0000 | 0.5904, 1.0000 |

CI confidence interval.

## DISCUSSION

The current study demonstrated that PET/CT imaging with 148 MBq of $^{64}$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 (Figs. 1 and 2) to facilitate high interreader and intrareader agreement on the presence or absence of metastatic or localized

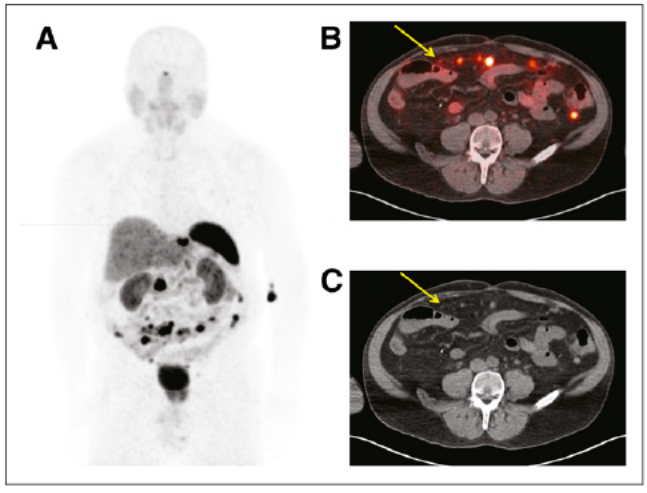


**FIGURE 1.** (A) Maximum intensity projection PET image of patient with metastatic small bowel carcinoid tumor. (B and C) Small omental (arrow) and peritoneal tumor implants are visible in PET/CT (B) and corresponding CT (C) images.

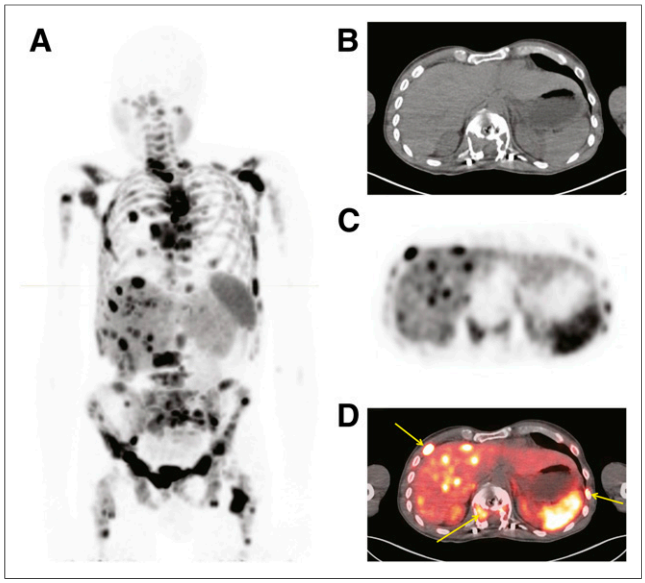


**FIGURE 2.** (A) Maximum intensity projection PET image of patient with metastatic bronchial carcinoid and extensive metastatic disease, including multiple small liver metastases. (B and C) Corresponding CT (B), PET (C), and PET/CT (D) images showing multiple bone metastases (arrows).

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 instance misread by the SOT oncologist must be considered to accurately gauge the diagnostic performance of $^{64}$Cu DOTATATE in this study. This misread might have been avoided with use of multiple oncologists or a multidisciplinary team to establish the SOT. However, we believe that use 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, $^{64}$Cu labeled ligands for PET imaging of NETs have been investigated in only a few studies (*7 9*). Of the available studies on patients with NETs, the first in humans 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 did $^{111}$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 did $^{68}$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 approximately 185 MBq (5 mCi) dose (*7 9*).

A strength of our study is the inclusion of many (21/63) NET negative healthy volunteers. The preestablished 2:1 (positive to negative) ratio translates to a more robust determination of diagnostic performance, which was bolstered by the high interreader ($\kappa = 0.76$) and intrareader 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 than of $^{68}$Ga DOTATATE (12.7 vs. 1.1 h) and centralized production may allow for wider geographic distribution, more flexible patient scheduling, and less strain for nuclear medicine technologists who must coordinate radioisotope 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 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 peptide receptor radionuclide therapy, as well as aid in clarifying suspect findings observed on initial scans. Also, the 12.7 h 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 than of $^{68}$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.

## DISCLOSURE

Research funding was provided by Curium and RadioMedix, Inc. Ebrahim S. Delpassand, David Ranganathan, Nilesh Wagh, Ali Abbasi, Andreas Kjaer, and Izabela Tworowska are employees and equity holders of RadioMedix. Andreas Kjaer is inventor on a

patent covering $^{64}$Cu DOTATATE PET for imaging of NETs in humans. No other potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGMENTS

Editorial assistance was provided, under the direction of the authors, by John Lapolla and Chris Ontiveros, PhD (Synchrony Group, West Chester, Pennsylvania), and statistical assistance was provided by Dennis Clason (Statking Consulting, Fairfield, Ohio).

## KEY POINTS

**QUESTION:** Is $^{64}$Cu DOTATATE PET/CT a potential alternative to $^{68}$Ga labeled SSTR tracers for imaging in patients with NETs?

**PERTINENT FINDINGS:** The current study was the first U.S. phase III, prospective, reader masked clinical trial and was con ducted on a total of 63 subjects 42 patients with suspected or confirmed SSTR positive NETs and 21 healthy volunteers known to be true negative. The study confirmed an ALARA optimal dose for diagnostic quality images at a lower (than previously pub lished) 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:** $^{64}$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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The Journal of NUCLEAR MEDICINE

# $^{64}$Cu-DOTATATE PET/CT for Imaging Patients with Known or Suspected Somatostatin Receptor–Positive Neuroendocrine Tumors: Results of the First U.S. Prospective, Reader-Masked Clinical Trial

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

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SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

NDA 213227

**NDA APPROVAL**

RadioMedix, Inc.
Attention: David Ranganathan, Ph.D.
Director, CMC and Regulatory Affairs
9701 Richmond Avenue, Suite 222
Houston, TX 77042

Dear Dr. Ranganathan:

Please refer to your new drug application (NDA) dated December 31, 2019, received January 3, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Detectnet (copper Cu 64 dotatate injection).

This new drug application provides for the use of Detectnet (copper Cu 64 dotatate injection) as a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adults.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling Prescribing Information, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on August 26, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "Final Printed Carton and Container Labeling for approved NDA 213227." Approval of this submission by FDA is not required before the labeling is used.

## ADVISORY COMMITTEE

Your application for Detectnet was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[6]

## POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at 301-796-1348.

Sincerely,

*{See appended electronic signature page}*

Charles Ganley,M.D.
Office Director
Office of Specialty Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[6] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use Detectnet safely and effectively. See full prescribing information for Detectnet.**

**Detectnet (copper Cu 64 dotatate injection), for intravenous use**

**Initial U.S. Approval: 2020**

**----------INDICATIONS AND USAGE----------**

Detectnet is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult patients. (1)

**----------DOSAGE AND ADMINISTRATION----------**

- Recommended dose is 148 MBq (4 mCi) administered as an intravenous bolus injection. (2.2)
- Begin acquiring images 45 to 90 minutes after drug administration. (2.4)
- See full prescribing information for additional preparation, administration, imaging and dosimetry information. (2)

**----------DOSAGE FORMS AND STRENGTHS----------**

- Injection: 148 MBq (4 mCi) (37 MBq (1 mCi) per 1 mL) of copper Cu 64 dotatate in a single-dose vial. (3)

**----------CONTRAINDICATIONS----------**

None. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- Radiation Risk: Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure (5.1). Advise patients to hydrate before and after administration and to void frequently after administration. (2.3)
- Risk for Image Misinterpretation: Uptake of Detectnet can be seen in a variety of tumor types other than NETs, in other pathologic conditions, and as a normal physiologic variant (e.g., uncinate process of the pancreas). (5.2)

**----------ADVERSE REACTIONS----------**

Reported adverse reactions include nausea, vomiting, and flushing. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Radiomedix Inc. at 1-800-535-5053 or pharmacovigilance@radiomedix.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**

Somatostatin Analogs: Somatostatin analogs competitively bind to the same somatostatin receptors as copper Cu 64 dotatate and may affect imaging. Image patients just prior to dosing with somatostatin analogs. For patients on long-acting somatostatin analogs, a wash-out period of 28 days is recommended prior to imaging. For patients on short-acting somatostatin analogs, a washout period of 2 days is recommended prior to imaging. (2.3, 7.1)

**----------USE IN SPECIFIC POPULATIONS----------**

Lactation: Advise patients to interrupt breastfeeding for 12 hours after Detectnet administration. (8.2).

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 9/2020**

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## FULL PRESCRIBING INFORMATION: CONTENTS*



* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Detectnet is indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult patients.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Radiation Safety – Drug Handling

Handle Detectnet with appropriate safety measures to minimize radiation exposure *[see Warnings and Precautions (5.1)]*. Use waterproof gloves, effective radiation shielding and appropriate safety measures when preparing and handling Detectnet.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

### 2.2 Recommended Dosage and Administration Instructions

Recommended Dosage

In adults, the recommended amount of radioactivity to be administered for PET imaging is 148 MBq (4 mCi) administered as an intravenous injection over a period of approximately 1 minute.

Administration

- Use Detectnet within 2 hours after calibration time.
- Use aseptic technique and radiation shielding when withdrawing and administering Detectnet.
- Inspect Detectnet visually for particulate matter and discoloration before administration. Do not use the drug if the solution contains particulate matter or is discolored.
- Calculate the necessary volume to administer based on measured activity, volume, calibration time, and date.
- Use a dose calibrator to measure the patient dose immediately prior to administration of Detectnet.
- After injection of Detectnet, administer an intravenous flush of 0.9% sodium chloride injection, USP.
- Dispose of any unused drug in a safe manner in compliance with applicable regulations.

### 2.3 Patient Preparation

Somatostatin Analogs

Image patients just prior to dosing with somatostatin analogs.

For patients on long-acting somatostatin analogs, a wash-out period of 28 days is recommended prior to imaging.

For patients on short-acting somatostatin analogs, a washout period of 2 days is recommended prior to imaging *[see Drug Interactions (7.1)]*.

Patient Hydration

Instruct patients to drink water to ensure adequate hydration prior to administration of Detectnet and to continue to drink and void frequently during the first hours following administration to reduce radiation exposure *[see Warnings and Precautions (5.1)]*.

Pregnancy Status

Assessment of pregnancy status is recommended in females of reproductive potential before administering Detectnet.

### 2.4 Image Acquisition

For Detectnet PET imaging, a whole-body acquisition from the skull vertex to mid-thigh is recommended. Image acquisition can begin between 45 to 90 minutes after the intravenous administration of Detectnet. Adapt Detectnet uptake time and scan duration according to the equipment used and the patient and tumor characteristics, to obtain the optimal image quality.

### 2.5 Image Interpretation

Copper Cu 64 dotatate binds to somatostatin receptors. Based upon the intensity of the signals, PET images obtained using copper Cu 64 dotatate injection indicate the presence and density of somatostatin receptors in tissues. Uptake can also be seen in a variety of non-NET tumors that contain somatostatin receptors or as a normal physiologic variant *[see Warnings and Precautions (5.2)]*. NET tumors that do not bear somatostatin receptors will not be visualized.

### 2.6 Radiation Dosimetry

Estimated radiation absorbed doses per injected activity for organs and tissues of adult patients following an intravenous administration of copper Cu 64 dotatate injection are shown in Table 1.

**Table 1. Estimated radiation absorbed dose per injected activity in selected organs with copper Cu 64 dotatate injection**

| Target Organ | Mean* absorbed dose (mGy/MBq) |
|---|---|
| Adrenals | 0.137 |
| Brain | 0.013 |
| Breasts | 0.013 |
| Gallbladder wall | 0.040 |
| Lower large intestine wall | 0.043 |

| | |
|---|---|
| Small intestine | 0.066 |
| Stomach wall | 0.019 |
| Upper large intestine wall | 0.022 |
| Heart wall | 0.019 |
| Kidneys | 0.139 |
| Liver | 0.161 |
| Lungs | 0.017 |
| Muscle | 0.019 |
| Ovaries | 0.019 |
| Pancreas | 0.093 |
| Red marrow | 0.027 |
| Osteogenic cells | 0.034 |
| Skin | 0.012 |
| Spleen | 0.115 |
| Testes | 0.014 |
| Thymus | 0.015 |
| Thyroid | 0.014 |
| Urinary bladder wall | 0.037 |
| Uterus | 0.019 |
| Total body | 0.025 |
| Effective dose (mSv/MBq) | 0.032 |

* Mean of 5 patients.

The effective radiation dose resulting from the administration of 148 MBq (4 mCi) to an adult is about 4.7 mSv. For an administered activity of 148 MBq (4 mCi) the typical radiation dose to the critical organs, which are the liver, the kidneys/adrenals, and the spleen, are about 24 mGy, 21 mGy and 17 mGy, respectively. Because the spleen has one of the highest physiological uptakes, higher uptake and radiation dose to other organs or pathologic tissues may occur in patients with splenectomy.

## 3 DOSAGE FORMS AND STRENGTHS

Injection; sterile, clear, colorless to yellow solution in a single-dose vial containing 148 MBq (4 mCi) (37 MBq (1 mCi) per 1 mL) of copper Cu 64 dotatate at calibration date and time.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Radiation Risk

Diagnostic radiopharmaceuticals, including Detectnet, contribute to a patient's overall long-term

cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. Advise patients to hydrate before and after administration and to void frequently after administration *[see Dosage and Administration (2.1, 2.3)]*.

### 5.2 Risk for Image Misinterpretation

The uptake of copper Cu 64 dotatate reflects the level of somatostatin receptor density in NETs, however, uptake can also be seen in a variety of other tumors that also express somatostatin receptors. Increased uptake might also be seen in other non-cancerous pathologic conditions that express somatostatin receptors including thyroid disease or in subacute inflammation, or might occur as a normal physiologic variant (e.g. uncinate process of the pancreas) *[see Dosage and Administration (2.5)]*.

A negative scan after the administration of Detectnet in patients who do not have a history of NET disease does not rule out disease *[see Clinical Studies (14)]*.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In safety and efficacy trials, 71 subjects received a single dose of Detectnet. Of these 71 subjects, 21 were healthy volunteers and the remainder were patients with known or suspected NET.

The following adverse reactions occurred at a rate of < 2%:

- *Gastrointestinal Disorders*: nausea, vomiting
- *Vascular Disorders*: flushing

In published clinical experience, 126 patients with known history of NET received a single dose of copper Cu 64 dotatate injection. Four patients were reported to have experienced nausea immediately after injection.

## 7 DRUG INTERACTIONS

### 7.1 Somatostatin Analogs

Non-radioactive somatostatin analogs and copper Cu 64 dotatate competitively bind to somatostatin receptors (SSTR2). Image patients just prior to dosing with somatostatin analogs. For patients on long-acting somatostatin analogs, a wash-out period of 28 days is recommended prior to imaging. For patients on short-acting somatostatin analogs, a washout period of 2 days is recommended prior to imaging *[see Dosage and Administration (2.3)]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

All radiopharmaceuticals, including Detectnet have the potential to cause fetal harm depending on the

fetal stage of development and the magnitude of the radiation dose. Advise a pregnant woman of the potential risks of fetal exposure to radiation from administration of Detectnet.

There are no data on Detectnet use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. No animal reproduction studies have been conducted with copper Cu 64 dotatate injection.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### 8.2 Lactation

Risk Summary

There are no data on the presence of copper Cu 64 dotatate in human milk, the effect on the breastfed infant, or the effect on milk production. Lactation studies have not been conducted in animals.

Advise a lactating woman to interrupt breastfeeding for 12 hours after Detectnet administration in order to minimize radiation exposure to a breastfed infant.

### 8.4 Pediatric use

The safety and effectiveness of Detectnet have not been established in pediatric patients.

### 8.5 Geriatric use

Clinical studies of Detectnet did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

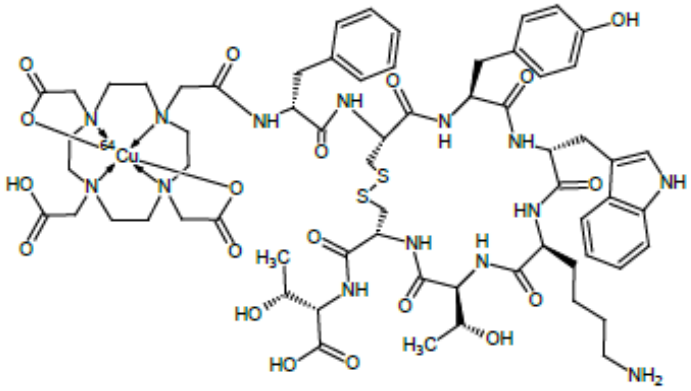
## 10 OVERDOSAGE

In the event of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by reinforced hydration and frequent bladder voiding. A diuretic might also be considered. If possible, estimation of the radioactive dose given to the patient should be performed.

## 11 DESCRIPTION

### 11.1 Chemical Characteristics

Detectnet contains copper Cu 64 dotatate, which is a radioactive diagnostic drug for use with PET imaging. Chemically, copper Cu 64 dotatate is described as copper (Cu 64)-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl) acetyl]-Dphenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic (2-7) disulfide. The molecular weight is 1497.2 Daltons and the following is the structural formula:



Detectnet is a sterile, clear, colorless to yellow solution for intravenous use. Each 10 mL single-dose vial contains 148 MBq (4 mCi) of copper Cu 64 dotatate at calibration date and time in 4 mL solution volume. Additionally, each mL of the solution contains 40 mg ascorbic acid, 0.05 ml of dehydrated alcohol, USP (ethanol) in sterile water for injection, USP. The pH is adjusted with sodium hydroxide, hydrochloric acid and is between 5.5 to 7.5.

### 11.2 Physical Characteristics

Table 2 and Table 3 display the principal radiation emission data and physical decay of copper Cu 64.

Copper Cu 64 decays with a half-life $t_{1/2}$=12.7 hours:

- 17.6% by positron emission to Ni 64 followed by emission of two 511 keV annihilation photons,
- 38.5% by beta decay to Zn 64,
- 43.8% by electron capture to Ni 64, and
- 0.475% by gamma radiation/internal conversion.

**Table 2. Principal radiation emission data (>1%) of copper Cu 64**

| Radiation/Emission | % Disintegration | Mean Energy (keV) |
|---|---|---|
| Positron ($\beta^+$) | 17.6 | 278 |
| Beta ($\beta^-$) | 38.5 | 190.7 |
| Gamma ($\gamma$) | 35.7 | 511 |
| | 0.48 | 1346 |

**Table 3. Physical decay chart of copper Cu 64**

| Hours | Fraction Remaining | Hours | Fraction Remaining |
|---|---|---|---|
| 0 | 1.00 | 18 | 0.374 |
| 1 | 0.947 | 24 (1 day) | 0.270 |
| 3 | 0.849 | 36 (1.5 days) | 0.140 |
| 6 | 0.721 | 48 (2 days) | 0.073 |
| 9 | 0.612 | 72 (3 days) | 0.020 |
| 12 | 0.520 | 96 (4 days) | 0.005 |

### 11.3 External Radiation

Gamma constant: 3.6 X $10^{-5}$ mSv/hr per MBq at 1 meter (0.133 mrem/hr per mCi at 1meter)

Table 4 displays the radiation attenuation by lead shielding of copper Cu 64.

**Table 4. Radiation attenuation of copper Cu 64 by lead shielding**

| Shield Thickness cm of Lead (Pb) | Coefficient of Attenuation |
|---|---|
| 0.51 | 0.5 |
| 1.60 | 0.1 |
| 3.45 | 0.01 |
| 6.83 | 0.001 |

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Copper Cu 64 dotatate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSTR2). It binds to cells that express somatostatin receptors including malignant neuroendocrine cells, which overexpress SSTR2 receptors. Copper Cu 64 is a positron ($\beta^+$) emitting radionuclide with an emission yield that allows positron emission tomography (PET) imaging.

### 12.2 Pharmacodynamics

The relationship between copper Cu 64 dotatate plasma concentrations and successful imaging was not explored in clinical trials.

### 12.3 Pharmacokinetics

Distribution

After 1 to 3 hours of a single dose administration of copper Cu 64 dotatate injection, the maximum radioactivity is observed in adrenal glands, kidney, pituitary glands, spleen, and liver.

Elimination

*Metabolism*

The metabolism of copper Cu 64 dotatate is unknown.

*Excretion*

Following a single intravenous dose (4.15 ± 0.13 mCi) of Detectnet (n = 6), between 16% to 40% radioactivity of the injected dose was recovered in urine over a 6-hour collection time.

Specific Populations

The effect of hepatic impairment or renal impairment on copper Cu 64 dotatate pharmacokinetics has not been studied.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with copper Cu 64 dotatate injection; however, radiation is a carcinogen and mutagen.

No animal studies were conducted to determine the effects of copper Cu 64 dotatate on fertility or embryology.

## 14 CLINICAL STUDIES

The efficacy of Detectnet was established in two single-center, open-label studies. Study 1 prospectively evaluated a total of 63 subjects, including 42 patients with known or suspected NET based on histology, conventional imaging, or clinical evaluations and 21 healthy volunteers. Of the 42 patients, 37 (88%) had a history of NETs at the time of Detectnet imaging. Among the total study population of 63 subjects, 28 (44%) were men and 35 (56%) were women with most subjects being white (86%). The mean age of the subjects was 54 years (range 25 to 82 years).

Detectnet images from each subject were interpreted as either positive or negative for NET by three independent readers who were blinded to clinical information and other imaging results. PET imaging results were compared to a composite reference standard consisting of a single oncologist's blinded assessment of subject diagnosis based on available histopathology results, reports of conventional imaging (MRI, contrast CT, bone scintigraphy, F 18 fludeoxyglucose PET/CT, F 18 sodium fluoride PET/CT, In 111 pentetreotide SPECT/CT, Ga 68 dotatate PET/CT) performed within 8 weeks prior to Detectnet imaging, and clinical and laboratory data including chromogranin A and serotonin levels. The proportion of subjects positive for disease per composite reference who were identified as positive by Detectnet imaging was used to quantify positive percent agreement. The proportion of subjects without disease per composite reference who were identified as negative by Detectnet imaging was used to quantify negative percent agreement. Table 5 shows the performance of Detectnet in the detection of NET for Study 1.

**Table 5: Performance of Detectnet in the detection of NET by reader in Study 1**

| | NET status as identified by reader | Reference | |
|---|---|---|---|
| | | Positive | Negative |
| Reader 1 (n=62)* | Positive | 30 | 1 |
| | Negative | 3 | 28 |
| | | | |
| | Percent Reader Agreement (95% CI)** | 91 (75, 98) | 97 (80, 99) |
| | | | |
| Reader 2 (n=63) | Positive | 30 | 6 |
| | Negative | 3 | 24 |
| | | | |
| | Percent Reader Agreement (95% CI)** | 91 (75, 98) | 80 (61, 92) |
| | | | |
| Reader 3 (n=63) | Positive | 30 | 3 |
| | Negative | 3 | 27 |
| | | | |
| | Percent Reader Agreement (95% CI)** | 91 (75, 98) | 90 (72, 97) |

n: number of patients, CI: confidence interval, *Reader 1 interpreted one of the 63 PET scans as "not evaluable", **Wilson score interval with continuity correction

Study 2 showed similar performance through retrospective analysis of published data collected in 112 patients (63 males, 49 females; mean age 62 years, range 30 to 84 years) with a known history of NET.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Detectnet (NDC 69945-064-01) is supplied as a sterile, clear, colorless to yellow solution in a 10 mL single-dose vial containing 148 MBq (4 mCi) (37 MBq (1 mCi) per mL) of copper Cu 64 dotatate at calibration date and time.

The sealed vial is contained in a shielded (lead) container for radiation protection. The product is shipped in a Type A package.

Discard unused portion from the single-patient use vial.

Storage and Handling

Store Detectnet in an upright position within the lead shielding to protect handlers from exposure to radiation.

Store Detectnet at controlled room temperature 20°C to 25°C (68°F to 77°F). Do not use and discard Detectnet 2 hours after the calibration date and time.

This radiopharmaceutical is for distribution and use by persons under license by the U.S. Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State. Store and dispose of Detectnet in compliance with the appropriate regulations of the government agency authorized to license the use of this radionuclide.

## 17 PATIENT COUNSELING INFORMATION

Radiation Risk

Advise patients to drink water to ensure adequate hydration prior to their PET study and recommend they drink and urinate as often as possible during the first hours following the administration of Detectnet, in order to reduce radiation exposure *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

Pregnancy

Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with Detectnet *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a lactating woman to interrupt breastfeeding for 12 hours after Detectnet administration in order to minimize radiation exposure to a breastfed infant *[see Use in Specific Populations (8.2)]*.

Manufactured, Packed and Distributed by:
Curium US LLC
2703 Wagner Place
Maryland Heights, MO 63043

# Detectnet™
(copper Cu 64 dotatate injection)

NDC 69945-064-01

**148 MBq (4 mCi) per 4 mL at calibration**
**(37 MBq (1 mCi) per 1 mL)**

For Intravenous Use Only.

Single-Dose Vial - Discard Unused Portion.

**Rx only**

Recommended adult dosage: 148 MBq (4 mCi) - See Prescribing Information.

Each mL contains: 37 MBq (1 mCi) of copper Cu 64 dotatate at calibration date and time, 40 mg ascorbic acid, 0.05 ml of dehydrated alcohol (ethanol) in sterile water for injection. Sodium hydroxide and / or hydrochloric acid is added for pH adjustment.

Store upright at controlled room temperature 20°C to 25°C (68°F to 77°F) in a shielded container.

CURIUM™

Manufactured, packed, and distributed by:
Curium US LLC, 2703 Wagner Place, Maryland Heights, MO 63043

R08/2020

A064C0

Reference ID: 4666138

Detectnet™
(copper Cu 64 dotatate injection)

Total Activity: 148 MBq (4 mCi) at calibration

Total Volume: 4 mL

Cal. time: 1700 CT

Cal. date: DDMMMYY

Exp. time: 1900 CT

Exp. date: DDMMMYY

Lot #:1234567890 10 digits

0959109SN9010LL# 1980#

CAUTION
RADIOACTIVE MATERIAL

Detectnet™
(copper Cu 64 dotatate injection)

Total Activity: 148 MBq (4 mCi) at calibration

Total Volume: 4 mL

Cal. time: 1700 CT

Cal. date: DDMMMYY

Exp. time: 1900 CT

Exp. date: DDMMMYY

Lot #:1234567890 10 digits

0959109SN9010LL# 1980#

CURIUM™

CAUTION
RADIOACTIVE MATERIAL

# Detectnet™
(copper Cu 64 dotatate injection)

Sterile

NDC 69945-064-01

**148 MBq (4 mCi) per 4 mL at calibration**
**(37 MBq (1 mCi) per 1 mL)**
**For Intravenous Use Only**
**Single-Dose Vial - Discard Unused Portion.**

**Cal. time:** 1700 CT
**Cal. date:**
DDMMMYY

**Exp. time:** 1900 CT
**Exp. date:**
DDMMMYY

**Lot #:** 1234567890 10 digits

**Recommended Dosage:**
See Prescribing Information

**Rx only**

Store upright at controlled room temperature 20°C to 25°C (68°F to 77°F) in a shielded container.

Manufactured, packed, and distributed by:
Curium US LLC
2703 Wagner Place
Maryland Heights, MO 63043

CAUTION RADIOACTIVE MATERIAL

A064 V0 R082020

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/s/

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CHARLES J GANLEY
09/03/2020 12:34:51 PM