JOURNAL OF CLINICAL ONCOLOGY

Prospective Study of ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites

Samira M. Sadowski, Vladimir Neychev, Corina Millo, Joanna Shih, Naris Nilubol, Peter Herscovitch, Karel Pacak, Stephen J. Marx, and Electron Kebebew

Listen to the podcast by Dr Strosberg at www.jco.org/podcasts

All authors: National Institutes of Health, Bethesda, MD.

Corresponding author: Electron Kebebew, MD, Chief Endocrine Oncology Branch, National Cancer Institute, National Institutes of Health Clinical Research Center, Building 10-CRC, Bethesda, MD 20892; e-mail: electron.kebebew@nih.gov.

ABSTRACT

Purpose

Gastro-entero-pancreatic neuroendocrine tumors (GEPNETs) are increasing in incidence, and accurate staging is important for selecting the appropriate treatment. ^{68}Ga-DOTATATE imaging is a promising approach for detecting GEPNETs and could help in selecting optimal therapeutic strategies. The aim of this study was to prospectively determine the clinical utility of ^{68}Ga-DOTATATE positron emission tomography (PET)/computed tomography (CT) in detecting unknown primary and metastatic GEPNETs.

Patients and Methods

One hundred thirty-one patients were enrolled in a prospective study of patients undergoing ^{68}Ga-DOTATATE PET/CT, ^{111}In-pentetreotide single-photon emission computed tomography (SPECT)/CT and multiphasic CT scan, and/or magnetic resonance imaging in a blinded fashion with comprehensive biochemical testing. The primary outcome measure was the detection of lesions by each imaging study.

Results

^{68}Ga-DOTATATE PET/CT imaging detected 95.1% of lesions (95% CI, 92.4% to 96.8%) with an average maximum standardized uptake value of 65.4 ± 47 (range, 6.9 to 244), anatomic imaging detected 45.3% of lesions (95% CI, 37.9% to 52.9%), and ^{111}In-pentetreotide SPECT/CT detected 30.9% of lesions (95% CI, 25.0% to 37.5%), with a significant difference between imaging modalities ($P < .001$). In four of 14 patients (28.6%), ^{68}Ga-DOTATATE PET/CT found a previously unknown primary tumor, and detected primary GEPNET, lymph node, and distant metastases correctly in 72 of 113 lesions (63.7%) when compared with histopathology, with 22.1% and 38.9% detected by using ^{111}In-pentetreotide SPECT/CT and anatomic imaging, respectively. On the basis of findings with ^{68}Ga-DOTATATE PET/CT, 43 of 131 patients (32.8%) had a change in management recommendation. In patients with carcinoid symptoms but negative biochemical testing, ^{68}Ga-DOTATATE PET/CT detected lesions in 65.2% of patients, 40% of which were detected neither by anatomic imaging nor by ^{111}In-pentetreotide SPECT/CT.

Conclusion

^{68}Ga-DOTATATE PET/CT imaging provides important information for accurate staging of GEPNETs and selection of appropriate treatment interventions even in the absence of biochemical evidence of disease in symptomatic patients.

J Clin Oncol 34:588-596. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that arise from the cells of the endocrine system. The incidence of gastro-entero-pancreatic NETs (GEPNETs) is about 7.8 per 100,000 persons/y with a prevalence of 35 per 100,000 persons.[1,2] Most GEPNETs are sporadic, but can be part of a familial cancer syndrome, such as multiple endocrine neoplasia type 1, neurofibromatosis type 1, von Hippel-Lindau, and tuberous sclerosis complex.[3-5]

The clinical presentation of GEPNETs depends on the anatomic sites involved, tumor biology, and functional status. Surgical resection

is the only curative treatment option for patients with early-stage disease; however, the extent, timing, and effect of surgical intervention for advanced, metastatic GEPNETs remain controversial. Most management guidelines emphasize that resection should be the first-line treatment option for patients with advanced GEPNETs if up to 90% of the disease burden is resectable[6]; however, only 5% to 20% of patients with advanced GEPNETs meet this criterion.[7,8] The identification of metastatic disease and tumor grade are the most important prognostic factors in patients with advanced GEPNETs.[9,10] Therefore, precise staging and evaluation of disease burden with a reliable imaging method is crucial for determining the best treatment strategy, especially as there are new treatment alternatives for locally advanced and metastatic GEPNETs.

A unique feature of NETs is the expression of somatostatin receptors (SSTR),[11,12] which can be targeted with radiolabeled peptides for imaging and treatment.[13] Imaging modalities currently approved by the US Food and Drug Administration (FDA) for evaluation of patients with GEPNETs include ^{111}In-pentetreotide single-photon emission computed tomography (SPECT)/computed tomography (CT) scintigraphy with a diagnostic sensitivity of 65% to 100%, depending on tumor site,[14,15] ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET), ^{123}I-metaiodobenzylguanidine scintigraphy, CT, and endoscopic ultrasound and magnetic resonance imaging (MRI). A relatively new PET/CT technique using somatostatin analogs labeled with the positron emitting isotope, ^{68}Ga (^{68}Ga-DOTA peptides), has been shown to offer advantages over conventional imaging modalities as well as additional important quantitative and qualitative diagnostic information.[16,17] This makes it an important tool in the clinical decision-making process for patients with GEPNETs.[18] 68Ga-DOTA imaging is still investigational in the United States and there have been no large prospective studies with comprehensive biochemical screening to evaluate its clinical utility when specifically focused on GEPNETs.

We conducted a prospective study to assess the clinical utility of ^{68}Ga-DOTATATE imaging for detecting unknown primary tumors and metastatic disease in patients with suspected or known GEPNETs with comprehensive biochemical testing, and compared it to current FDA-approved imaging modalities, ^{111}In-pentetreotide SPECT/CT, CT, and/or MRI.

PATIENTS AND METHODS

Patients

Patients suspected or known to have GEPNETs on imaging (CT, MRI, ^{18}F-FDG PET) and/or biochemical evidence of GEPNETs, and/or a familial predisposition to NET (multiple endocrine neoplasia type 1 or von Hippel-Lindau) were included. The study was performed under an Investigational New Drug approval from the FDA, and Eligibility criteria are outlined in Table 1. The study was approved by the National Cancer Institute Institutional Review Board and the National Institutes of Health Radiation Safety Committee (NCT01967537). Written informed consent was obtained from all study participants.

Biochemical and Imaging Evaluation in Patients With GEPNET

All patients underwent testing for serum chromogranin A, pancreatic polypeptide, neuron-specific enolase and vasoactive intestinal polypeptide, urinary 5-hydroxyindoleacetic acid (5-HIAA), and fasting serum gastrin, somatostatin, insulin, C-peptide (proinsulin), and glucagon.

Table 1. Study Eligibility Criteria

Factors Determining Eligibility

Inclusion criteria
  Patient with any one of the following:
    Suspicion of NET on imaging (CT/MRI/^{18}F-FDG PET); and/or
    Biochemical evidence of NET (serum/urinary) on the basis of elevated levels of chromogranin A, pancreatic polypeptide, neuron-specific enolase, vasoactive intestinal polypeptide, serotonin (urinary 5-HIAA), gastrin, somatostatin, catecholamines, metanephrines, calcitonin, fasting insulin, C-peptide (proinsulin), glucagon; and/or
    Familial predisposition to NET in patient with clinical or genetic proof of mutation in *MEN1* or *VHL* (symptomatic and/or asymptomatic case; with biochemical or anatomic imaging evidence of disease).
  Age ≥ 18 years.
  For women: Negative urine pregnancy test or postmenopausal for at least 2 years or if patient has had a hysterectomy.
  Patient must be willing to return to NIH for follow-up.
  Ability of patient or legally authorized representative (if the patient is deemed by the treating physician to be cognitively impaired or questionably impaired in such a way that the ability of the patient to give informed consent is questionable) to understand and the willingness to sign a written informed consent document indicating that he or she is aware of the investigational nature of this study.
Exclusion criteria
  Patient unwilling to undergo serial noninvasive imaging.
  Pregnant or lactating woman: Pregnant women are excluded from this study because the effects of ^{68}Ga-DOTATATE in pregnancy are not known. Because there is an unknown but potential risk for adverse events in nursing infants secondary to administration of ^{68}Ga-DOTATATE in the mother, breastfeeding should be discontinued for at least 1 day if the mother receives ^{68}Ga-DOTATATE.
  Patient has recognized concurrent active infection.
  Patient has had the use of any investigational product or device, excluding F-DOPA scans, within 30 days before dosing.

Abbreviations: CT, computed tomography; ^{18}F-FDG, ^{8}F-fluorodeoxyglucose; 5-HIAA, 5-hydroxyindoleacetic acid; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NIH, National Institutes of Health; PET, positron emission tomography; VHL, von Hippel-Lindau.

For ^{68}Ga-DOTATATE PET/CT imaging, ^{68}Ga-DOTATATE 185 MBq (5 mCi) was administered through a peripheral vein. After approximately 60 minutes, the patient was positioned supine in a PET/CT scanner, and images were obtained from the area of the upper thighs to midskull. A low-dose, noncontrast enhanced CT was used for attenuation correction and anatomic localization. Maximum standardized uptake values (SUV_{max}) were measured on the basis of patient total body weight. Patients treated with long-acting octreotide were scanned before the next scheduled monthly dose.[19]

An ^{111}In-pentetreotide SPECT/CT scan was performed after intravenous administration of ^{111}In-pentetreotide 222 MBq (6 mCi) within 4 weeks of ^{68}Ga-DOTATATE PET/CT. Planar whole body ^{111}In-pentetreotide with SPECT/CT scans of the chest (at 24 hours) and abdomen and pelvis (at 4 hours and repeated at 24 hours) were used for analyses. A low-dose, noncontrast enhanced CT was used for attenuation correction and anatomic localization. Anatomic imaging (chest, abdominal, and pelvic CT scan) was performed using LightSpeed Ultra and LightSpeed QX/i scanners (General Electric Healthcare Technologies, Waukesha, WI) as well as an Mx8000 IDT scanner (Philips Medical Systems, Andover, MA) with the following settings: noncontrast, arterial and portal venous phase, 2-mm slices, with rapid infusion of nonionic, water-soluble contrast agent (130 mL injected at 2 mL/s), and oral contrast. In patients with severe contrast allergy (n = 6) or renal insufficiency (n = 4), an abdominal and pelvic MRI was performed, with slices at a thickness of 6 mm, to include T2 series with and without fat saturation and short tau inversion recovery and T1 pre- and postcontrast series, after intravenous injection of gadolinium-diethylentriamine pentaacetic acid (Siemens Verio 1.5 Tesla; Siemens Medical Solution, Malvern, PA; and Philips Achieva 1.5 and 3 Tesla; Philips Medical Systems). One hundred seven patients had all three imaging studies

within 14 days, 15 patients within 1 month, and 9 patients had the CT scan within 3 months of the two functional imaging modalities.

Data Analyses

Images were reviewed independently by radiology and nuclear medicine physicians in a blinded fashion. All imaging studies were analyzed and correlated with clinical information in an unblinded fashion by a multidisciplinary team to determine the optimal treatment. Treatment strategies took into account the functional status of GEPNET, risk of malignancy (primary tumor size and grade), and/or the presence of metastatic disease.

Patient-to-patient and lesion-to-lesion analyses were performed. Body areas were analyzed separately and grouped as pancreas, liver, bowel, lung and mediastinum (parenchyma and lymph nodes), abdomen and retroperitoneal lymph nodes (excluding liver, pancreas, adrenal glands, and bowel), and bone. The neck and brain area were excluded from data analysis, as no initial anatomic brain scan was performed for comparison. Because of the known physiologic uptake of ^{68}Ga-DOTATATE in the spleen and adrenal glands, these organs were also excluded from analysis.

The total number of lesions on all three imaging modalities was taken to be the imaging denominator and this number represents the sum of lesions of all anatomic and functional imaging. Two analyses were performed, one in the entire study cohort and one in patients who underwent surgery with histopathologic diagnosis.

Statistical Analyses

Statistical analyses were performed using GraphPad Prism 5 software (GraphPad Software, La Jolla, CA). Data of continuous variables are presented as mean ± standard deviation (SD) or median (range). Spearman rank correlation coefficient (r) was used to measure and test the association of two continuous variables. Differences in proportions between subgroups of patients were compared by using the two-sample binomial test. Generalized estimating equations with a logit link function and working independence correlation structure were used to estimate and compare the proportions of positive lesions between ^{68}Ga-DOTATATE and ^{111}In-pentetreotide as well as between ^{68}Ga-DOTATATE and CT/MRI. The standard errors of the proportions and the Wald test were based on robust variance estimates under a working independence model assumption. Generalized estimating equations analysis was done using R version 3.1.0 and the R package *geepack* (The R Project for Statistical Computing, Vienna, Austria). A two-tailed P value $<$ .05 was considered statistically significant.

RESULTS

Study Cohort Biochemical Profile and Imaging Results

The clinical and biochemical characteristics of the study cohort are summarized in Table 2. A total of 131 patients with biochemical or radiologic suspicion and/or known diagnosis of GEPNET were enrolled. Serum chromogranin A and urinary 5-HIAA levels correlated with the number of lesions detected with ^{68}Ga-DOTATATE PET/CT imaging (r = 0.46; P < .001; n = 128; and r = 0.43; P < .001; n = 119, respectively; Figs 1A and 1B). There was a weak correlation between serum neuron-specific enolase level and the number of lesions (r = 0.22; P = .016; n = 123). There was also a correlation between chromogranin A and 5-HIAA and the number of lesions on CT/MRI and ^{111}In-pentetreotide SPECT/CT scanning (chromogranin A: r = 0.54; P < .001; and r = 0.49; P <001; 5-HIAA: r = 0.32; P < .001; and r = 0.32; P < .001, respectively). Levels of chromogranin A and 5-HIAA were significantly higher in patients with liver metastases (Mann-Whitney P = .005 and P < .001, respectively; Figs 1C and 1D).

| **Table 2.** Clinical and Biochemical Characteristics of Study Cohort	
Characteristic	Value
No. of patients	131
Male-to-female ratio	1:1.3
Mean age ± SD, years (range)	51 ± 15 (19-82)
Patients by symptom type, No. (%)	
Total*	72 (55.0)
Flushing	30 (22.9)
Diarrhea	26 (19.8)
Wheezing/shortness of breath	3 (2.3)
Abdominal pain	10 (7.6)
Rash/itching	2 (1.5)
Median fasting chromogranin A, ng/mL (range)	87.5 (20-18,710)
Normal median fasting chromogranin A, ng/mL	< 93
Median fasting gastrin, pg/mL (range)	28 (10-17,290)
Normal median fasting gastrin, pg/mL	< 100
Median fasting neuron-specific enolase, ng/mL (range)	9.2 (5-45)
Normal median fasting neuron-specific enolase, ng/mL	≤ 15
Median fasting pancreatic polypeptide, pg/mL (range)	108.5 (40-2,500)
Normal median fasting pancreatic polypeptide, pg/mL	< 291
Median urinary 5-HIAA, mg/24 hours (range)	4.9 (0.9-211)
Normal median urinary 5-HIAA, mg/24 hours	≤ 8
Mean SUVmax on ^{68}Ga-DOTATATE PET/CT ± SD, range	65.4 ± 47.2 (6.9-244)
Patients with prior histologically proven NET, No. (%)	89 (68.5)
Instances of previous surgery by tumor type, No. (%)	
Total	69 (77.5)
Pancreatic NET	31 (44.9)
Gastro-enteric NET	38 (55.1)
Type of prior proven NETs, No. (%)*	
Pancreatic NET	36 (27.5)
Small/large bowel NET	31/4 (23.7/3.0)
Insulinoma	7 (5.3)
Gastric NET	7 (5.3)
Thymic carcinoid†	1 (0.8)
Vipoma	2 (1.5)
Lung NET†	1 (0.8)
^{68}Ga-DOTATATE PET/CT found primary, No. (%)	4/14 (28.6)
Surgery recommended, No. (%)‡	19 (14.5)
PRRT recommended, No. (%)	11 (8.4)

Abbreviations: CT, computed tomography; 5-HIAA, 5-hydroxyindoleacetic acid; NET, neuroendocrine tumor; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SD, standard deviation; SUV$_{max}$, maximum standardized uptake value.

*Some patients had more than one symptom or site of tumor manifestation. Sites were scored separately.

†Patients with multiple endocrine neoplasia type 1 and gastro-entero-pancreatic NET that have additional manifestations, such as thymic carcinoid or lung NET.

‡On the basis of ^{68}Ga-DOTATATE PET/CT.

The proportion of positive lesions in the study cohort is summarized in Table 3. ^{68}Ga-DOTATATE PET/CT detected 95.1% of lesions (95% CI, 92.4% to 96.8%) with an average SUV$_{max}$ of 65.4 ± 47 (range, 6.9 to 244), corresponding to 847 of 891 total lesions identified by the imaging denominator. This was significantly higher than anatomic imaging (CT and/or MRI; 404 of 891 lesions; 45.3% [95% CI, 37.9% to 52.9%]) and ^{111}In-pentetreotide SPECT/CT (275 of 891 lesions; 30.9% [95% CI, 25.0% to 37.5%]). In 37 patients (28.2%), the imaging results were discordant: ^{111}In-pentetreotide SPECT/CT (n = 36) and CT scan (n = 12) were negative and ^{68}Ga-DOTATATE PET/CT was positive, and, in one patient, two duodenal lesions were seen using ^{111}In-pentetreotide
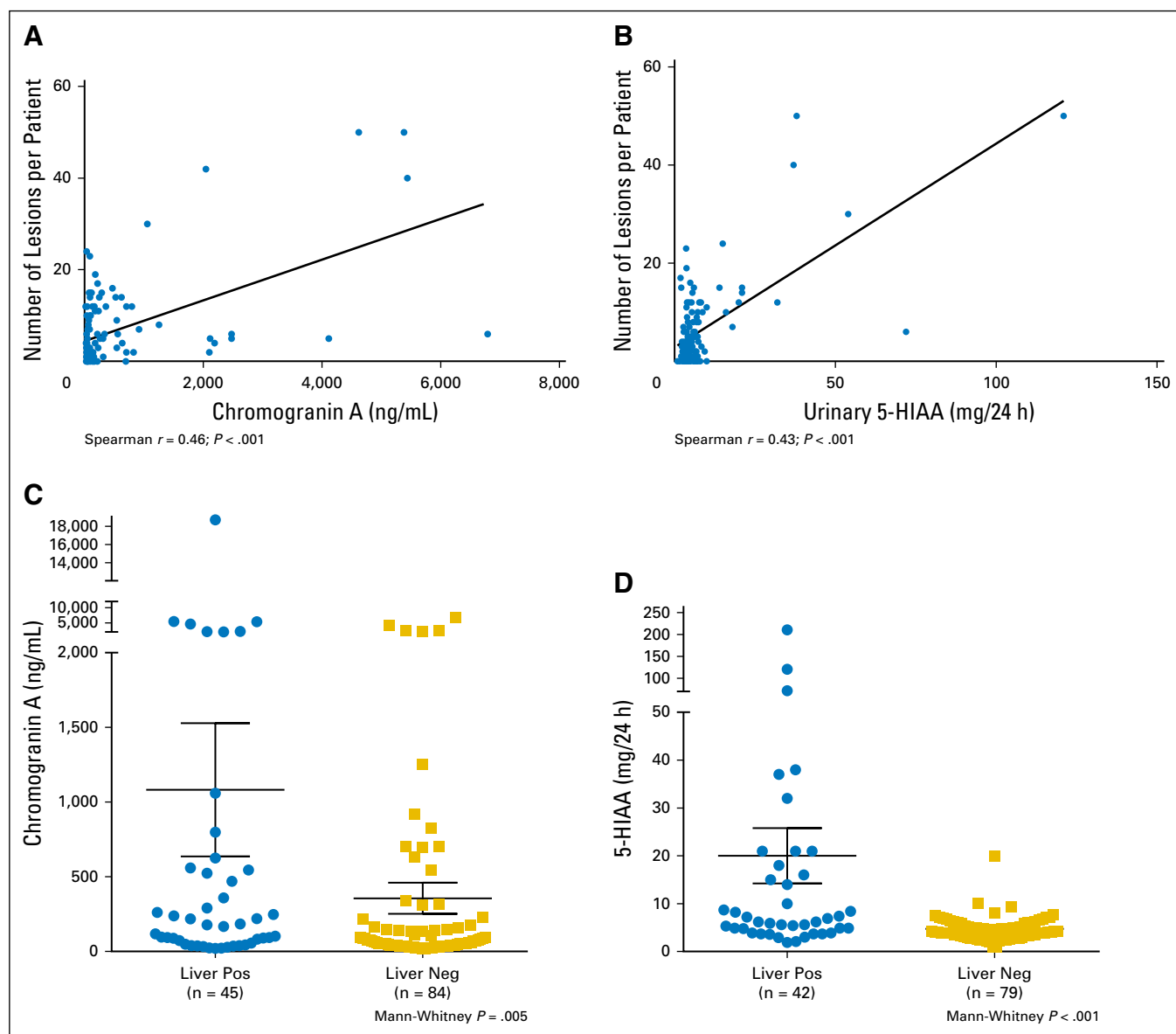
Fig 1. There was a significant correlation between (A) chromogranin A and (B) 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) and the number of lesions per patient found by using 68Ga-DOTATATE positron emission tomography (PET)/computed tomography (CT) imaging (Spearman coefficient $r = 0.46$; $P < .001$; n = 128; and $r = 0.43$; $P < .001$; n = 119, respectively). Mean (C) chromogranin A and (D) 24-hour urinary 5-HIAA were significantly higher in patients with liver metastases present with 68Ga-DOTATATE PET/CT imaging (chromogranin A: liver positive [pos] 1083 ± 446 v liver negative [neg] 356 ± 104; Mann-Whitney $P = .005$; and 5-HIAA: liver positive 20 ± 5.8 v liver negative 4.7 ± 0.3; Mann-Whitney $P < .001$).

SPECT/CT only. Four hundred twenty-two lesions were detected by 68Ga-DOTATATE PET/CT imaging that were missed both by 111In-pentetreotide SPECT/CT and CT/MRI scans.

Fourteen patients had an unknown primary tumor, and in four patients the primary lesion was found by using 68Ga-DOTATATE PET/CT imaging, but was not seen with 111In-pentetreotide SPECT/CT, and in two of four patients it was not seen on CT/MRI. An example is shown in Figures 2A to 2E, in which 68Ga-DOTATATE PET/CT imaging confirmed known liver metastases and showed a small bowel primary tumor and a periaortic lymph node with a SUV$_{max}$ of 75.

An analysis of 23 patients who had no biochemical evidence of GEPNETs but who had possible hormone-related symptoms, such as flushing and diarrhea (Table 1), showed that 68Ga-DOTATATE

PET/CT imaging detected more lesions than did 111In-pentetreotide SPECT/CT (15 of 23 lesions [65.2%] v six of 23 lesions [26.1%]; $P = .02$) and CT/MRI (15 of 23 lesions [65.2%] v nine of 23 lesions [39.1%]; $P = .14$). CT/MRI missed liver lesions in four patients and duodenal and small bowel lesions in two patients, and 111In-pentetreotide SPECT/CT scanning missed liver lesions in three additional patients. Of 25 patients with hormonal-related symptoms and biochemical evidence of disease that had no prior proven diagnosis of NET, and in whom 68Ga-DOTATATE PET/CT imaging detected lesions, seven patients had negative findings with 111In-pentetreotide SPECT/CT imaging and three patients had negative findings using CT/MRI. In four of these patients, all three imaging modalities were negative.

Table 3. Proportion of Positive Lesions Detected by ^{68}Ga-DOTATATE PET/CT, ^{111}In-Pentetreotide SPECT/CT, and CT Scan on the Basis of Lesions Identified by Imaging Denominator

Lesion by Compartment	^{68}Ga-DOTATATE PET/CT		^{111}In-Pentetreotide SPECT/CT		Anatomic Imaging (CT and/or MRI)		P (^{68}Ga-DOTATATE v ^{111}In-Pentetreotide)	P (^{68}Ga-DOTATATE v CT/MRI)
	No. of Lesions Found (imaging denominator)	Proportion of Positive Lesions, % (95% CI)	No. of Lesions Found (imaging denominator)	Proportion of Positive Lesions, % (95% CI)	No. of Lesions Found (imaging denominator)	Proportion of Positive Lesions, % (95% CI)		
Total	847 (891)	95.1 (92.4 to 96.8)	275 (891)	30.9 (25.0 to 37.5)	404 (891)	45.3 (37.9 to 52.9)	< .001	< .001
Pancreas	105 (110)	95.5 (89.4 to 98.1)	22 (110)	20 (12.8 to 29.8)	59 (110)	53.6 (42.8 to 64.2)	< .001	< .001
Liver	396 (408)	97.1 (93.7 to 98.7)	170 (408)	41.7 (31.1 to 53.1)	233 (408)	57.1 (44.7 to 68.7)	< .001	< .001
Bowel	49 (51)	96.1 (75.9 to 99.5)	7 (51)	13.7 (5.4 to 30.7)	6 (51)	11.8 (3.6 to 32.6)	< .001	< .001
Lung and mediastinum	30 (40)	75 (54.4 to 88.3)	16 (40)	40 (25.3 to 56.7)	30 (40)	75 (53.0 to 88.9)	.003	1.0
Abdomen and retroperitoneal lymph node	144 (153)	94.1 (87.1 to 97.4)	41 (153)	26.8 (16.6 to 40.2)	60 (153)	39.2 (29.7 to 49.6)	< .001	< .001
Bone	123 (129)	95.3 (82.5 to 98.9)	19 (129)	14.7 (6.4 to 30.6)	16 (129)	12.4 (7.3 to 20.3)	< .001	< .001

NOTE. Imaging denominator represents the sum of functional and anatomic imaging.
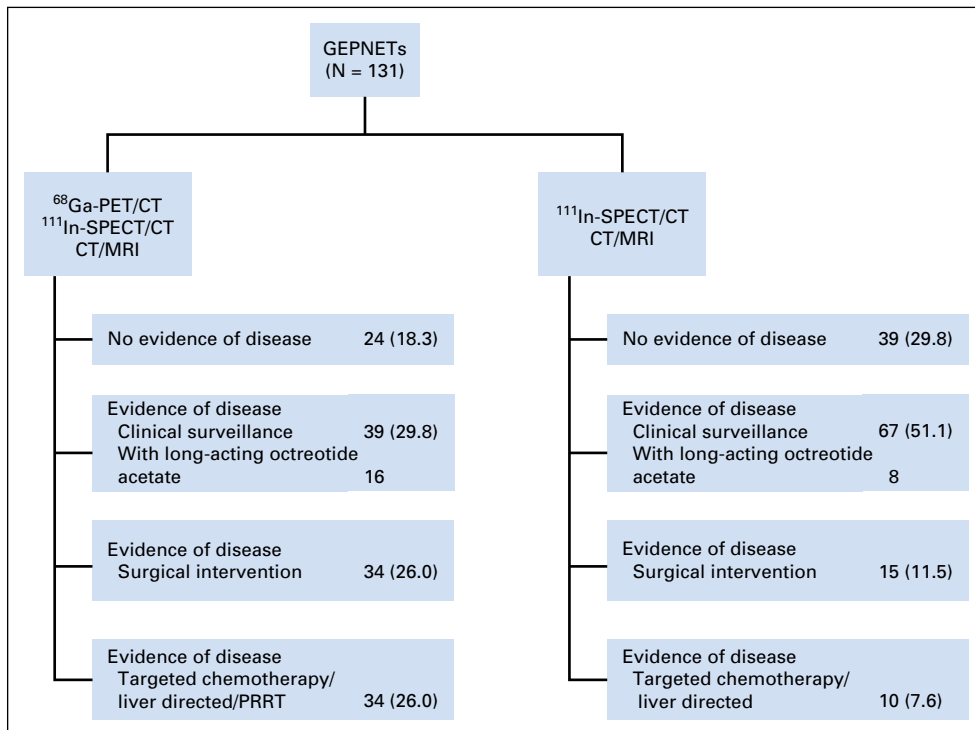Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.
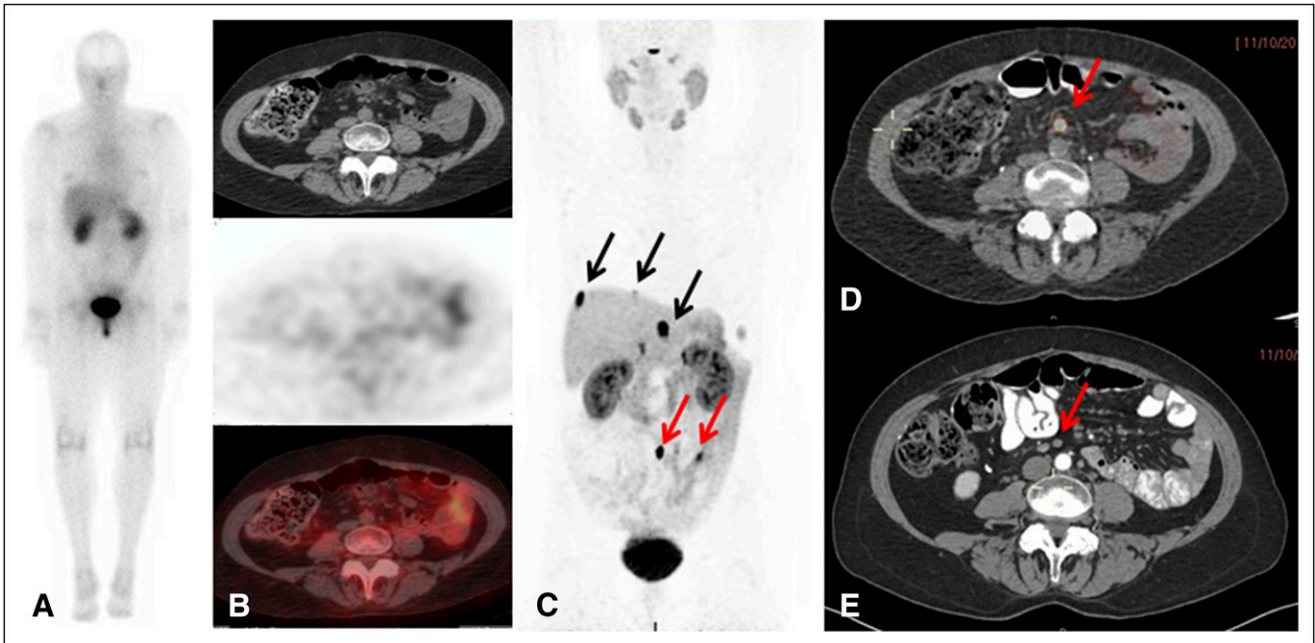
Fig 2. A case of a patient with known liver metastases and previously unknown primary lesion detected by ⁶⁸Ga-DOTATATE positive emission tomography (PET)/ computed tomography (CT). (A) ¹¹¹In-Pentetreotide scan (planar) shows no pathologic uptake. (B, top) Axial CT, (middle) ¹¹¹In-pentetreotide axial slice, and (bottom) fused single-photon emission CT/CT showing no pathologic uptake. (C) ⁶⁸Ga-DOTATATE PET maximum-intensity projection image shows three liver metastases (black arrows) and two lesions in the abdomen (lymph node and enteric lesion; red arrows). (D) ⁶⁸Ga-DOTATATE PET/CT image shows the mesenteric lymph node (maximum standardized uptake value, 75; red arrow). (E) Arterial phase CT shows corresponding small indeterminate lymph node (red arrow).

Surgical resection of primary tumors and/or metastases was recommended in 34 of 131 patients (26%). Of these, 25 patients had undergone surgery at the time of data analysis. The histopathologic findings are summarized in Appendix Tables A1 and A2 (online only). On histopathology, 113 lesions were found to be positive for GEPNET, with 37 lesions (32.7%) being primary tumors and with 69 lymph nodes (61.1%) and seven distant metastases (6.2%). When we compared ⁶⁸Ga-DOTATATE PET/CT imaging to surgical histopathology in a per-lesion analysis, we found true positive lesions in 72 of 113 lesions (63.7%), in 25 of 113 lesions

Fig 3. Clinical management diagram on the basis of the three imaging modalities. Data are given as No. (%). CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SPECT, single-photon emission computed tomography.

(22.1%) with ^{111}In-pentetreotide SPECT/CT imaging, and in 44 of 113 lesions (38.9%) with CT/MRI. All 38 lesions not detected by imaging studies but proven on histopathology represented lymph node metastases.

Impact of Imaging Results on Clinical Management

In 97 patients, we recommended nonsurgical management that included clinical and radiologic follow-up in a time period of 6 months to 1 year (63 patients), liver-directed therapy (four patients), and peptide receptor radionuclide therapy (PRRT; 11 patients) or systemic therapy with everolimus or sunitinib (19 patients).

Upon comparing the different imaging findings and evaluating their impact on clinical management, we found that, compared with ^{111}In-pentetreotide SPECT/CT, ^{68}Ga-DOTATATE PET/CT imaging detected additional lesions in 93 of 131 patients (71.0%), and in 69 of 131 patients (52.7%) compared with CT scan. Of those, in 44 of 93 patients (47.3%) and in 34 of 69 patients (49.2%), these additional lesions consisted of metastatic lesions found by using ^{68}Ga-DOTATATE PET/CT imaging. These additional findings led to a change in management in 43 of 131 patients (32.8%). An example of a patient with additional lesions that were found by using ^{68}Ga-DOTATATE PET/CT but that were not seen on ^{111}In-pentetreotide SPECT/CT and CT scan is shown in Appendix Figure A1 (online only), and the specific changes in management recommendation as a result of ^{68}Ga-DOTATATE PET/CT imaging are shown in Figure 3.

DISCUSSION

Our results show that ^{68}Ga-DOTATATE PET/CT scanning is superior to ^{111}In-pentetreotide SPECT/CT and anatomic imaging in the detection of unknown primary tumors and primary and metastatic GEPNETs. ^{68}Ga-DOTATATE PET/CT had a detection rate of 95.2% compared with detection rates of 45.6% and 30.9% for anatomic and ^{111}In-pentetreotide SPECT/CT imaging, respectively. ^{68}Ga-DOTATATE PET/CT identified primary tumors in 28.6% of patients with previously unknown primary tumors. Furthermore, this led to the alteration of patient management recommendations in 32.8% of patients. ^{68}Ga-DOTATATE PET/CT also detected disease in patients without biochemical evidence of GEPNET and in those with symptoms and no biochemical evidence of disease.

We found that serum chromogranin A, urinary 5-HIAA, and serum neuron-specific enolase correlated with the number of tumors found by using ^{68}Ga-DOTATATE PET/CT in patients with GEPNET, and that chromogranin A and 5-HIAA were elevated in patients with liver metastases. These findings are consistent with data in the literature, in which serum chromogranin A and urinary 5-HIAA have been associated with tumor burden and patient survival.[20,21] Of interest, we show that ^{68}Ga-DOTATATE PET/CT imaging was helpful in detecting disease in 15 of 23 symptomatic patients (65.2%) with biochemically negative workups, offering a rationale with treatment possibilities for their otherwise unexplained symptoms.

^{68}Ga-DOTATATE PET/CT detected significantly more lesions in the bowel and bone when compared with ^{111}In-pentetreotide

SPECT/CT and CT/MRI scanning, with ^{111}In-pentetreotide SPECT/CT detecting slightly more lesions than CT/MRI. This difference was significant again for the pancreas, liver, and lymph nodes in the abdomen and retroperitoneal compartment. Furthermore, we showed that ^{68}Ga-DOTATATE PET/CT imaging performed as well as anatomic imaging (CT/MRI) in detecting lesions in the lung and mediastinal compartment, suggesting that these two imaging modalities could be complementary for staging patients with GEPNET and suspected lung metastases.

The use of ^{68}Ga-DOTATATE PET/CT has been recommended for staging[22] and for detecting early recurrences after resection of NET,[23] and its impact on medical and surgical management strategies has been shown in retrospective studies.[18,24] On the basis of ^{68}Ga-DOTATATE PET/CT imaging, Hofman et al[18] reported a change in treatment plan in 47% of patients with NET, and Ilhan et al[25] found additional information for surgical planning in 95% of cases with small bowel (ileum) or pancreatic NET, which resulted in changes in management in one fifth of patients.

To our knowledge, the current study is the largest prospective study of ^{68}Ga-DOTATATE PET/CT in a homogenous cohort of patients with GEPNETs. There have been four prospective studies, one with a mixed cohort of 19 patients with NET using ^{68}Ga-DOTATATE,[26] and three other studies with different ^{68}Ga-DOTA peptides: two using ^{68}Ga-DOTATOC in a mixed cohort of 84 and 27 patients with NET, including lung NETs, neuroblastoma, and paraganglioma, and one using ^{68}Ga-DOTANOC in 109 patients with GEPNET. All four prospected studies showed the superiority of ^{68}Ga-DOTA peptide imaging compared with conventional scintigraphy and anatomic imaging.[27-29] Our study results are consistent with these studies but provide additional new data. First, two thirds of patients with symptoms of carcinoid syndrome and no biochemical evidence of disease were found to have lesions by using ^{68}Ga-DOTATATE PET/CT imaging. Second, our management recommendations changed on the basis of real-time assessment of the burden of disease in patients and a standardized management algorithm. Last, our study shows that ^{68}Ga-DOTATATE was able to identify unknown primary GEPNET and disease in symptomatic patients without biochemical evidence of disease.

For progressive metastatic GEPNET, there are several therapeutic options, such as surgical resection and/or pharmacologic and liver-directed therapies. PRRT is a relatively new therapeutic modality that targets the positivity of SSTR in GEPNET as the treatment rationale, permitting targeted therapy with somatostatin analogs labeled with radionuclides. According to published guidelines, PRRT is indicated for the treatment of patients with positive expression of SSTR2, metastatic, or inoperable NET[30]; these are mainly patients with SSTR2-expressing GEPNETs and bronchial NETs. Large series have shown median progression-free survival of up to 40 months for PRRT with ^{177}Lu-DOTA-octreotate.[31] Therefore, it is important, when selecting treatment options, to use the ^{68}Ga-DOTA peptide PET/CT to stage patients with progressive, metastatic, and/or inoperable GEPNETs and to determine the tumor somatostatin receptor status. Furthermore, ^{68}Ga-DOTATATE PET/CT scanning has the advantage over ^{111}In-pentetreotide SPECT/CT in that it requires a shorter imaging time and has a lower cost[32] and radiation exposure (1.1 rem).[33]

Our study does have limitations. While most lesions detected by using ^{68}Ga-DOTATATE PET/CT imaging are likely to be true

positive findings on the basis of their high SUV and location, we do not have histopathologic proof for every lesion detected; thus, false positive results are possible. The study design—not a randomized controlled trial—and the lack of follow-up data does not allow us to definitively answer whether the therapeutic options selected on the basis of ^{68}Ga-DOTATATE PET/CT imaging resulted in improved long-term patient outcome. The number of lesions per patient found by using ^{68}Ga-DOTATATE PET/CT imaging is an approximation of tumor burden and is not a precise measurement of tumor mass/burden. In addition, the imaging denominator is not a perfect gold standard and could represent some false positive results. Furthermore, ^{68}Ga-DOTATATE PET/CT imaging is known to show lower disease avidity for poorly differentiated NET,[34] and it would therefore be beneficial for disease characterization to perform ^{18}F-FDG PET/CT imaging in these situations, as this could show higher avidity. Our study design did not include ^{18}F-FDG PET/CT imaging in every patient as part of the clinical research protocol, although we did perform it when clinically indicated. Furthermore, adding a diagnostic, contrast-enhanced CT scan might improve the sensitivity and specificity of SPECT/CT or PET/CT imaging to detect NET.

In conclusion, ^{68}Ga-DOTATATE PET/CT imaging is more sensitive for staging and detecting unknown primary GEPNETs than is ^{111}In-pentetreotide SPECT/CT and anatomic imaging with CT/MRI. Therefore, we believe it should be implemented in the initial management and follow-up of patients with GEPNETs as it can significantly optimize patient care decisions.

AUTHOR CONTRIBUTIONS

Conception and design: Samira M. Sadowski, Vladimir Neychev, Corina Millo, Peter Herscovitch, Karel Pacak, Stephen J. Marx, Electron Kebebew
Financial support: Electron Kebebew
Administrative support: Electron Kebebew
Provision of study materials or patients: Naris Nilubol, Electron Kebebew
Collection and assembly of data: Samira M. Sadowski, Vladimir Neychev, Corina Millo, Peter Herscovitch, Karel Pacak, Stephen J. Marx, Electron Kebebew
Data analysis and interpretation: Samira Sadowski, Vladimir Neychev, Corina Millo, Joanna Shih, Naris Nilubol, Karel Pacak, Stephen J. Marx, Electron Kebebew
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Tsikitis VL, Wertheim BC, Guerrero MA: Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: A SEER analysis. J Cancer 3:292-302, 2012

2. Lawrence B, Gustafsson BI, Chan A, et al: The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am 40:1-18, 2011 doi:10.1016/j.ecl.2010.12.005

3. Duh QY, Hybarger CP, Geist R, et al: Carcinoids associated with multiple endocrine neoplasia syndromes. Am J Surg 154:142-148, 1987

4. Charlesworth M, Verbeke CS, Falk GA, et al: Pancreatic lesions in von Hippel-Lindau disease? A systematic review and meta-synthesis of the literature. J Gastrointest Surg 16:1422-1428, 2012

5. Larson AM, Hedgire SS, Deshpande V, et al: Pancreatic neuroendocrine tumors in patients with tuberous sclerosis complex. Clin Genet 82:558-563, 2012

6. Plöckinger U, Rindi G, Arnold R, et al; European Neuroendocrine Tumour Society: Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours: A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology 80:394-424, 2004

7. Saxena A, Chua TC, Perera M, et al: Surgical resection of hepatic metastases from neuroendocrine neoplasms: A systematic review. Surg Oncol 21:e131-e141, 2012

8. Sutcliffe R, Maguire D, Ramage J, et al: Management of neuroendocrine liver metastases. Am J Surg 187:39-46, 2004

9. Yao JC, Hassan M, Phan A, et al: One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 26:3063-3072, 2008

10. Ramage JK, Davies AH, Ardill J, et al; UKNET-work for Neuroendocrine Tumours: Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 54:iv1-iv16, 2005 (suppl 4)

11. Reubi JC, Kvols L, Krenning E, et al: Distribution of somatostatin receptors in normal and tumor tissue. Metabolism 39:78-81, 1990 (suppl 2)

12. de Herder WW, Hofland LJ, van der Lely AJ, et al: Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. Endocr Relat Cancer 10:451-458, 2003

13. Reubi JC: Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 24:389-427, 2003

14. Rufini V, Calcagni ML, Baum RP: Imaging of neuroendocrine tumors. Semin Nucl Med 36:228-247, 2006

15. Kwekkeboom DJ, Krenning EP: Somatostatin receptor imaging. Semin Nucl Med 32:84-91, 2002

16. Falconi M, Bartsch DK, Eriksson B, et al; Barcelona Consensus Conference participants: ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: Well-differentiated pancreatic non-functioning tumors. Neuroendocrinology 95:120-134, 2012

17. Yang J, Kan Y, Ge BH, et al: Diagnostic role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with neuroendocrine tumors: A meta-analysis. Acta Radiol 55:389-398, 2014

18. Hofman MS, Kong G, Neels OC, et al: High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. J Med Imaging Radiat Oncol 56:40-47, 2012

19. Haug AR, Rominger A, Mustafa M, et al: Treatment with octreotide does not reduce tumor uptake of (68)Ga-DOTATATE as measured by PET/CT in patients with neuroendocrine tumors. J Nucl Med 52:1679-1683, 2011

20. van Adrichem RC, Hofland LJ, Feelders RA, et al: Chromogranin A, Ki-67 index and IGF-related genes in patients with neuroendocrine tumors. Endocr Connect 2:172-177, 2013

21. Nölting S, Kuttner A, Lauseker M, et al: Chromogranin a as serum marker for gastro-enteropancreatic neuroendocrine tumors: A single center experience and literature review. Cancers (Basel) 4:141-155, 2012

22. Virgolini I, Ambrosini V, Bomanji JB, et al: Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging 37:2004-2010, 2010

23. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al: Neuroendocrine tumor recurrence: Diagnosis with ^{68}Ga-DOTATATE PET/CT. Radiology 270:517-525, 2014

24. Frilling A, Sotiropoulos GC, Radtke A, et al: The impact of ^{68}Ga-DOTATOC positron emission tomography/computed tomography on the multi-modal management of patients with neuroendocrine tumors. Ann Surg 252:850-856, 2010

25. Ilhan H, Fendler WP, Cyran CC, et al: Impact of (68)Ga-DOTATATE PET/CT on the surgical management of primary neuroendocrine tumors of the pancreas or ileum. Ann Surg Oncol 22:164-171, 2015

26. Etchebehere EC, de Oliveira Santos A, Gumz B, et al: ^{68}Ga-DOTATATE PET/CT, ^{99m}Tc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: A prospective trial. J Nucl Med 55:1598-1604, 2014

27. Gabriel M, Decristoforo C, Kendler D, et al: ^{68}Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: Comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 48:508-518, 2007

28. Naswa N, Sharma P, Kumar A, et al: Gallium-68-DOTA-NOC PET/CT of patients with gastroentero-pancreatic neuroendocrine tumors: A prospective single-center study. AJR Am J Roentgenol 197:1221-1228, 2011

29. Buchmann I, Henze M, Engelbrecht S, et al: Comparison of ^{68}Ga-DOTATOC PET and ^{111}In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 34:1617-1626, 2007

30. Bodei L, Mueller-Brand J, Baum RP, et al: The joint IAEA, EANM, and SNMMI practical guidance

on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 40:800-816, 2013 [Erratum: Eur J Med Mol Imaging 41:584, 2014]

31. Kwekkeboom DJ, de Herder WW, Kam BL, et al: Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: Toxicity, efficacy, and survival. J Clin Oncol 26:2124-2130, 2008

32. Schreiter NF, Brenner W, Nogami M, et al: Cost comparison of ^{111}In-DTPA-octreotide scintigraphy

and ^{68}Ga-DOTATOC PET/CT for staging enteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 39:72-82, 2012

33. Walker RC, Smith GT, Liu E, et al: Measured human dosimetry of ^{68}Ga-DOTATATE. J Nucl Med 54:855-860, 2013

34. Kayani I, Bomanji JB, Groves A, et al: Functional imaging of neuroendocrine tumors with combined PET/CT using ^{68}Ga-DOTATATE (DOTA-DPhe1, Tyr3-octreotide) and ^{18}F-FDG. Cancer 112:2447-2455, 2008

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites

Samira M. Sadowski
No relationship to disclose

Vladimir Neychev
No relationship to disclose

Corina Millo
No relationship to disclose

Joanna Shih
No relationship to disclose

Naris Nilubol
No relationship to disclose

Peter Herscovitch
No relationship to disclose

Karel Pacak
No relationship to disclose

Stephen J. Marx
No relationship to disclose

Electron Kebebew
No relationship to disclose

Acknowledgment

Appendix

Table A1. Characteristics of Patients Who Underwent Surgery

Characteristic	Value
No. of patients	25
Mean age, years (range)	42 (21-73)
Male-to-female ratio	1.5:1
No. of sporadic tumors	11
No. of syndromic tumors	14
MEN1	10
VHL	4

Abbreviations: MEN1, multiple endocrine neoplasia type 1; VHL, von Hippel-Lindau.

Table A2. TNM Staging for Patients Who Underwent Surgery

Stage	Pancreatic NET (n = 16)*	Gastro-Entero-NET (n = 9)†
Tx	1	3
T0	2	1
T1	3	1
T2	7	3
T3	3	1
T4	0	0
N0	12	2
N1	4	7
M0	14	7
M1	2	2
WHO grade		
G1	6	5
G2	6	2
G3	1	0

*Bosman et al: Lyon, France, International Agency for Research on Cancer, 2010.
†Pape et al: Neuroendocrinology 95:135-156, 2012.
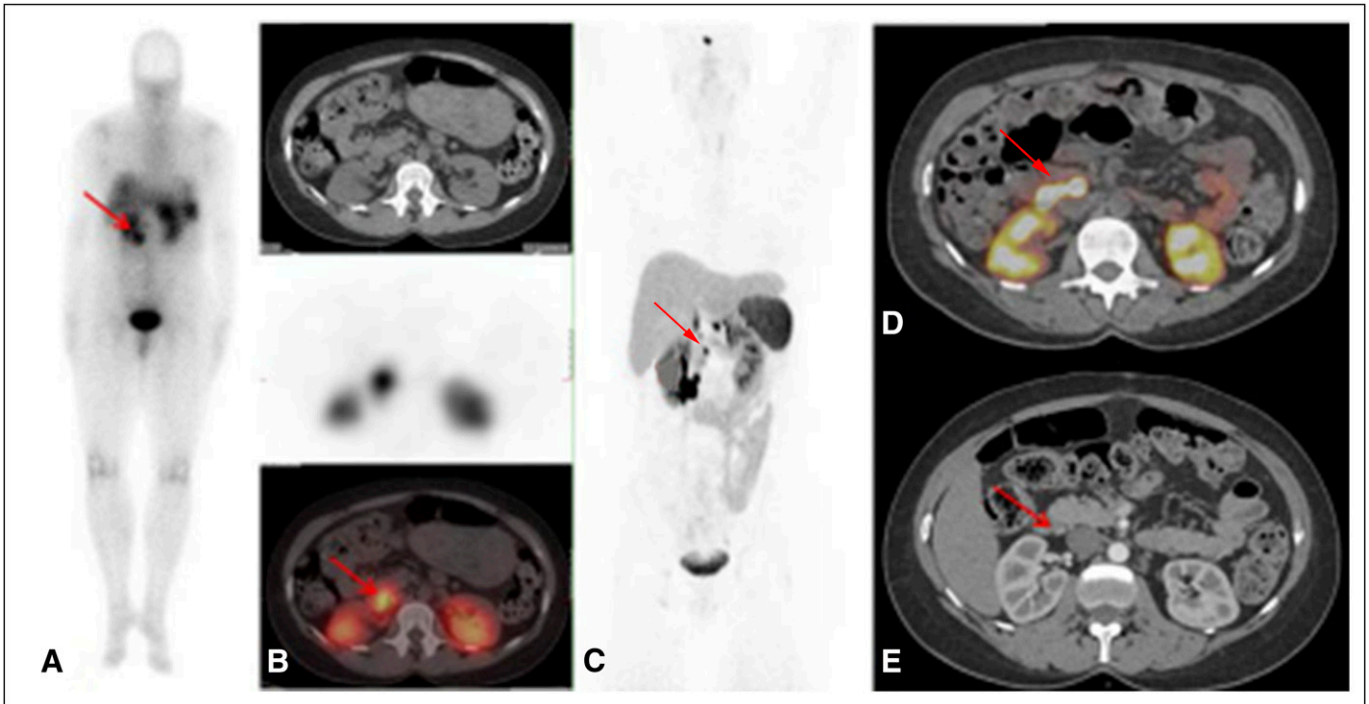
Fig A1. A 46-year-old patient with multiple endocrine neoplasia type 1 and known pancreatic and duodenal lesions who had lymph nodes not previously known that were detected by using ^{68}Ga-DOTATATE positron emission tomography (PET)/computed tomography (CT) imaging. (A) ^{111}In-Pentetreotide scan (planar) shows a unique unclear prerenal uptake. (B, top) Axial CT, (middle) ^{111}In-pentetreotide axial slice, and (bottom) fused single-photo emission CT/CT showing unclear pathologic uptake (red arrow). (C) ^{68}Ga-DOTATATE PET maximum-intensity projection image shows retropancreatic lymph node (red arrow) and duodenal and pancreatic lesions. (D) ^{68}Ga-DOTATATE Q: 17 PET/CT image shows the retropancreatic and periduodenal lymph node (maximum standardized uptake value, 96; red arrow). (E) Arterial phase CT shows corresponding lymph node (red arrow) that was read as a subcentimeter indeterminate lymph node.