The Role of ^{68}Ga-DOTATATE PET in Patients with Neuroendocrine Tumors and Negative or Equivocal Findings on ^{111}In-DTPA-Octreotide Scintigraphy

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[111]In-diethylenetriaminepentaacetic acid (DTPA)-octreotide scintigraphy is currently the nuclear medicine imaging modality of choice for identifying neuroendocrine tumors. However, there are cohorts of patients in whom scintigraphy findings are negative or equivocal. We evaluated the role of ^{68}Ga-DOTATATE PET in a selected group of patients with negative or weakly positive findings on ^{111}In-DTPA-octreotide scintigraphy to determine whether ^{68}Ga-DOTATATE PET is able to detect additional disease and, if so, whether patient management is altered. **Methods:** Fifty-one patients with a histologically confirmed diagnosis of neuroendocrine tumors were included. Of the 51 patients, 35 who were negative and 16 equivocal for uptake on ^{111}In-DTPA-octreotide scintigraphy underwent ^{68}Ga-DOTATATE PET. Findings were compared using a region-by-region analysis. All findings were verified with CT or MRI. After ^{68}Ga-DOTATATE PET, all cases were reviewed to determine whether the ^{68}Ga-DOTATATE PET findings resulted in any alteration in management, in terms of suitability for peptide receptor therapy, somatostatin analogs, and surgery. **Results:** Of the 51 patients, 47 had evidence of disease on cross-sectional imaging or biochemically. ^{68}Ga-DOTATATE PET was positive in 41 of these 47 patients (87.2%). No false-positive lesions were identified. ^{68}Ga-DOTATATE PET detected 168 of the 226 lesions (74.3%) that were identified with cross-sectional imaging. ^{68}Ga-DOTATATE PET identified significantly more lesions than ^{111}In-DTPA-octreotide scintigraphy ($P <$ 0.001). There was no correlation between ^{68}Ga-DOTATATE uptake and histologic grade of neuroendocrine tumors. ^{68}Ga-DOTATATE imaging changed management in 36 patients (70.6%), who were subsequently deemed suitable for peptide receptor–targeted therapy. **Conclusion:** In patients with negative or equivocal ^{111}In-DTPA-octreotide findings, ^{68}Ga-DOTATATE PET identifies additional lesions and may alter management in most cases.

Gastroenteropancreatic neuroendocrine tumors (NETs) are a heterogeneous group of relatively rare tumors. These tumors may arise from almost anywhere within the body but arise predominantly from the gastroenteropancreatic tract; they can metastasize to any organ (*1*). Somatostatin receptor (SSTR) overexpression in NETs has enabled development of imaging with scintigraphy using radiolabeled somatostatin analogs (*2,3*). To date, 5 SSTRs have been characterized, all of which are expressed in differing frequencies in NETs (*4*). SSTR-2 and -5 are expressed in 70%−90% of NETs (*5*). The most commonly used radiolabeled somatostatin analogs allow visualization and staging of carcinoid tumors expressing SSTR-2 and -5, though expression of other SSTR receptors can be identified with different analogs (*6*). The most commonly used radioligand is ^{111}In-diethylenetriaminepentaacetic acid (DTPA)–octreotide, which is commercially available as ^{111}In-pentetreotide. The expression of SSTRs in these tumors allows radionuclide therapy, subject to good uptake of somatostatin radiolabeled analogs. To date this expression has been assessed using ^{111}In-DTPA-octreotide scintigraphy (*7,8*).

^{111}In-DTPA-octreotide binds predominantly to SSTR-2–positive cells and emits γ-rays, which enable imaging of SSTR-2–positive NETs (*9*). The reported sensitivity of ^{111}In-DTPA-octreotide scintigraphy varies from 67% to 100% (*6,7,10,11*) and differs according to the type of NET being visualized. There are limitations with this technique, and it has a restricted ability to identify lesions

smaller than 1 cm and to obtain good spatial resolution, even when using SPECT (12).

In the last few years, studies using ^{68}Ga-DOTATOC PET in NETs have shown promising results, with a higher rate of lesion identification than is achieved with conventional ^{111}In-DTPA-octreotide scintigraphy (13–16). On the basis of availability at that time, in this study we used DOTATATE, an SSTR-2 analog (17), labeled with ^{68}Ga, a positron emitter. [68]Ga is produced from a [68]Ge–[68]Ga generator and therefore is not dependent on a cyclotron. The automated labeling of this radiopharmaceutical done according to good laboratory practice under sterile conditions in an isolator takes approximately 60 min. The yield of ^{68}Ga-DOTATATE is more than 98% with this method.

The study had 3 aims: first, to assess whether ^{68}Ga-DOTATATE PET identifies SSTR-2–positive disease in NET patients with negative or weakly positive ^{111}In-DTPA-octreotide findings; second, to establish whether there is any association between tumor grade and lesion identification using ^{68}Ga-DOTATATE PET; and finally, to evaluate whether ^{68}Ga-DOTATATE PET alters clinical management in patients with weak or negative ^{111}In-DTPA-octreotide findings.

MATERIALS AND METHODS

Study Population

From November 2006 to March 2008, 312 patients underwent ^{111}In-DTPA-octreotide scintigraphy. All were under prospective follow-up at the NET unit of Royal Free Hospital, London. Of these, 51 were referred for ^{68}Ga-DOTATATE PET because of scintigraphy findings that were negative or showed only low-grade uptake of tracer (Krenning score, <2) (18). Briefly, the scale for the Krenning score is as follows: 0 = no abnormality, 1 = faint uptake in the tumor; 2 = clear uptake in the tumor but less than in the liver; 3 = uptake greater in the tumor than in the liver; 4 = uptake much greater in the tumor than in the liver (18). Long-acting somatostatin analogs were not stopped before imaging with PET or ^{111}In-DTPA-octreotide scintigraphy.

We retrospectively reviewed the images and clinical data from the 51 patients (27 men and 24 women; age range, 18–80 y; median age, 55.5 y), who were imaged with ^{68}Ga-DOTATATE PET/CT between January 2007 and April 2008. Forty-five patients underwent chest, abdomen, and pelvis CT; 2 underwent abdomen MRI; and 4 underwent chest, abdomen, and pelvis CT and additional MRI of the liver. All patients gave informed consent, in line with local medical ethical guidance.

The primary tumor origin was as follows: medullary thyroid, 2; thymic carcinoids, 2; paraganglioma, 2; hindgut, 2; bronchus, 2; pancreas, 13; midgut, 22. The remaining 6 patients had cancer of unknown primary origin (Table 1). All patients had a previous histologic diagnosis of NET based on World Health Organization criteria. All had undergone scanning with ^{111}In-DTPA-octreotide within a median of 4 mo (range, 1–8 mo) of ^{68}Ga-DOTATATE PET. Histologic findings were available in all cases, and tumor grade was classified as low, intermediate, or high, using the proposed criteria of the European Neuroendocrine Tumour Society for grading gastroenteropancreatic NETs (19,20). The classi-

TABLE 1. Characteristics of Study Population

Characteristic	Data
Demographics	
Male	27
Female	24
Mean age (y)	55.5
Age range (y)	18–80
Primary origin (n)	
Bronchus	2
Thyroid	2
Thymus	2
Pancreas	13
Midgut	22
Hindgut	2
Paraganglioma	2
Unknown	6
Histologic grade (n)	
Low	28
Intermediate	19
High	4
Treatment (n)	
Current therapy with somatostatin analogs	27
Previous surgery	9
Previous chemotherapy	10

Histologic grade was determined using proposed guidelines of European Neuroendocrine Tumour Society and extrapolated to include thymic carcinoid, unknown primaries, and paraganglioma.

fication was extended to include tumors of other sites and cancer of unknown primary origin.

Image Acquisition

For ^{68}Ga-DOTATATE PET, images were acquired 1 h after injection of 120–200 MBq of ^{68}Ga-DOTATATE. No adverse effects were observed after the injection of ^{68}Ga-DOTATATE. Imaging was performed using a dedicated GE Discovery LS PET/CT unit; whole-body examinations (mid brain to mid thigh) were performed with the patient supine.

CT was performed using the four 3.75-mm detectors, a pitch of 1.5, and a 5-mm collimation. The CT exposure factors for all examinations were 140 kVp and 80 mA in 0.8 s. With patient position maintained, a whole-body PET emission scan was performed covering an area identical to that covered by CT; scans were performed in 3-dimensional mode. All PET acquisitions were carried out in 3-dimensional mode (4 min per bed position), in an approximately 30-min scanning time. PET images were reconstructed using CT for attenuation correction. Transaxial emission images of $4.3 \times 4.3 \times 4.25$ mm were reconstructed using ordered-subsets expectation maximization with 2 iterations and 28 subsets. The axial field of view was 148.75 mm, resulting in 35 slices per bed position.

For ^{111}In-DTPA-octreotide SPECT, patients were injected with 200 MBq of ^{111}In-pentetreotide IV (Covidien). Whole-body images were acquired at 24 h after injection on a dual-head γ-camera (Picker Prism; Phillips Medical Technology) using a medium-energy collimator. Patients were scanned with a camera speed of 7.2 cm/min and a matrix of $256 \times 1,024$. Photopeaks were set at 173 and 247 keV, with ±10% windows and no offset. SPECT abdominal images were obtained from the dome of the

liver downward. An additional chest or pelvic SPECT study was performed if warranted by the appearance of the whole body or if abnormalities had been identified previously in other areas on cross-sectional imaging. Scan parameters were as follows: medium-energy collimator, 60 stops per head at 3° intervals, 25 s per stop, 64 × 64 matrix. The same energy window was used as with planar imaging. Images were processed and analyzed at a workstation using Odyssey software (Phillips Medical Technology). They were reconstructed using an iterative ordered-subsets expectation maximization program with 6 iterations and processed with a count-optimized Butterworth filter. Images were displayed as a full data set of orthogonal slices of 9-mm thickness. Images from ^{111}In-DTPA-octreotide scintigraphy were reviewed by 2 nuclear medicine physicians.

The images from ^{68}Ga-DOTATATE PET/CT were reported in consensus by an experienced dedicated nuclear medicine physician and a dual-accredited radiologist/nuclear medicine physician, who were unaware of the results of the previous ^{111}In-DTPA-octreotide study. Areas of abnormal focal uptake were documented, with care taken to exclude sites of known physiologic activity on ^{68}Ga-DOTATATE PET and ^{111}In-DTPA-octreotide scintigraphy. These areas of abnormal uptake were compared with cross-sectional imaging to confirm the presence of lesions. The images from ^{111}In-DTPA-octreotide scintigraphy were reported independently by an experienced nuclear medicine physician. If any discrepancies were present in the reports of the 2 examiners, the images were reviewed together and a consensus reached.

A 3-phase CT scan was obtained (unenhanced, arterial-phase enhancement at 30 s after injection, and venous-phase enhancement at 70 s after injection). The liver alone is scanned before contrast enhancement, the chest and liver are scanned in the arterial phase, and the whole abdomen and pelvis are scanned in the venous phase. All scans were acquired at 120 kVp and variable amperage, depending on body habitus. We used a Brilliance 64-slice scanner (Phillips Medical Systems, DMC GmbH) or a Lightspeed scanner (GE Healthcare). Scans were reconstructed at 3-mm (Brilliance) or 5-mm (Lightspeed) intervals. Intravenous contrast material was used: 100 mL of Omnipaque 300 (GE Healthcare) administered via a pump injector (E-Z-EM) at 3.5 mL/s.

The MRI scanner was a 1.5-T Achieva (Phillips Medical Systems). All scans were acquired using the Synergy Sense body coil. Slice thickness was 7 mm, with a 0.7-mm interspace and a 512 × 512 matrix. The contrast medium was Dotarem (Guerbet), 0.2 mL/kg, infused at 1.5 mL/s with a 20-mL saline flush via a cannula in an antecubital vein using a pump injector (Medrad).

Interpretation of Data

The number of lesions that could be identified clearly as single foci was determined for each patient. To enable a methodic and consistent approach to lesion identification, we created 3 categories of lesion sites: organs (lungs, breast, liver, pancreas, gastrointestinal tract, kidney, spleen, and pelvis/ovaries), nodal regions (thoracic, mesenteric, abdominal, and pelvic [excluding mesenteric]), and musculoskeletal system (vertebrae, bony thorax, bony pelvis, and limb bones). The same anatomic areas were imaged with ^{68}Ga-DOTATATE PET and ^{111}In-DTPA-octreotide scintigraphy to ensure relevant comparison of lesion detection. Because of confluence and inability to clearly delineate single liver lesions in some cases, liver metastases were classified as 1 organ metastasis, independent of the number of liver metastases

present. Lymph nodes smaller than 1 cm on CT or MRI and showing marked avidity for ^{68}Ga-DOTATATE and ^{111}In-DTPA-octreotide were labeled as positive for disease.

The presence of lesions was confirmed by cross-sectional imaging of all patients with CT or MRI. Patients who underwent ^{68}Ga-PET had PET/CT to confirm the location of disease. Plasma chromogranin A levels were available for all patients, and where appropriate, fasting gut hormone levels and urinary 5-hydroxyindoleacetic acid were also measured.

Statistical Analysis

Statistical analysis was performed using Prism (version 5.00; GraphPad Software) for Windows (Microsoft). Because the values generally were not normally distributed, nonparametric tests were used to compare marker levels between groups, that is, the Mann–Whitney U test (for 2 groups).

RESULTS

In total, 51 patients underwent ^{68}Ga-DOTATATE PET and ^{111}In-DTPA-octreotide scanning. Of these, 47 had evidence of disease on cross-sectional imaging; the 4 remaining patients had undergone previous curative surgical resection and were receiving surveillance imaging. In the 47 patients with evidence of disease, a total of 226 lesions were identified on cross-sectional imaging (including MRI, CT, and PET/CT). The number of patients with lesions from each anatomic site is listed in Table 2. Thirty-five patients were negative for uptake on ^{111}In-DTPA-octreotide scintigraphy, whereas in the remaining 16 patients a total of 27 lesions were identified with a Krenning score of less than 2. ^{68}Ga-DOTATATE PET identified disease in 41 of 47 patients (87.2%) and detected 168 (74.3%) of the 226 lesions identified on cross-sectional imaging. The number of lesions seen in each organ with each modality is listed in Table 3.

Patient Analysis

Negative ^{111}In-DTPA-Octreotide Findings. Among the 51 patients, ^{111}In-DTPA-octreotide findings were negative, with no evidence of uptake (other than physiologic uptake) in 35 patients. In 3 of these 35 patients, no disease was identified on cross-sectional imaging and patients had normal chromogranin A and fasting gut hormone levels. The 3 patients with no evidence of disease on any modalities are considered to be disease-free currently; all of these patients had undergone previous surgical resection.

The remaining 32 patients had disease identified on cross-sectional imaging. Among these, ^{68}Ga-DOTATATE findings were positive in 27 (Fig. 1). In total, 97 lesions were identified in the 27 patients with positive ^{68}Ga-DOTATATE findings, whereas cross-sectional imaging identified 125 lesions in the 32 patients with disease.

Five patients who were negative for uptake on both ^{68}Ga-DOTATATE PET and ^{111}In-DOTA-octreotide scanning had evidence of disease on cross-sectional imaging. In these patients, 27 lesions were identified on CT ± MRI. These tumors were metastatic; the primary sites were ileal and pancreatic in 1 case each, whereas 3 were from unknown

TABLE 2. Total Number of Lesions Identified in Each Type of NET with the Different Modalities

Site	Tumor grade	No. of patients	111In-DTPA octreotide scintigraphy	68Ga-DOTATATE PET	Cross-sectional imaging
Bronchus	Low	1	1	1	1
	Intermediate	1	0	14	14
Thyroid	Low	1	0	0	1
	Intermediate	1	0	1	1
Thymus	Intermediate	1	0	1	4
	High	1	1	1	1
Pancreas	Low	9	12	22	25
	Intermediate	2	0	2	6
	High	2	1	4	5
Ileum	Low	12	7	40	48
	Intermediate	10	3	38	46
Paraganglioma	Low	1	1	17	17
	Intermediate	1	0	12	12
Unknown	Low	2	0	3	8
	Intermediate	3	0	7	17
	High	1	0	0	15
Hindgut	Low	2	1	5	5
Total patients or lesions		51*	27	168	226

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*Includes 4 patients with no evidence of disease on cross-sectional imaging.

primaries. Two patients had functional syndromes (both carcinoid), and the remaining 3 had no syndromic features. Histologic results from these 5 patients showed 2 with low-grade tumors, 2 with intermediate-grade tumors, and 1 with a high-grade tumor.

Low-Grade or Faint Uptake on 111In-DTPA-Octreotide Scintigraphy. In 16 patients, there was some uptake on 111In-DTPA-octreotide scintigraphy; however, the uptake in the extrahepatic lesion was of low grade and notably less than that in the liver. Cross-sectional evidence of disease was identified in 15 of these patients. In 1 patient, 111In-DTPA-octreotide scintigraphy identified mediastinal and left-lung uptake of very low grade. This uptake was commented on in view of the fact that the patient had medullary thyroid cancer, which had previously been resected. Subsequently, there was no residual disease on cross-sectional imaging or uptake on 68Ga-DOTATATE PET, and plasma tumor markers plus chromogranin A were normal. This was the only false-positive result seen among all 51 patients. Uptake on 68Ga-DOTATATE PET was seen in 14 of the 16 patients with low-grade uptake on 111In-DTPA-octreotide. A total of 101 lesions were identified with cross-sectional imaging in the 15 patients with disease; of these, 71 (70.3%) were identified with 68Ga-DOTATATE PET.

68Ga-DOTATATE PET was false-negative in 1 case, which was an intermediate-grade nonfunctional pancreatic tumor. In this patient, 111In-DTPA-octreotide scintigraphy showed faint uptake in the region of the gallbladder and liver, corresponding to the site of liver metastases.

The sensitivity of 111In-DTPA-octreotide scintigraphy was not determined in view of the bias of the sample population. The specificity of 111In-DTPA-octreotide scintigraphy was 98%, because there was only 1 false-positive

result. The sensitivity of 68Ga-DOTATATE PET was 87.2%, and the specificity was 100%.

Lesion Analysis

Evidence of NET disease was identified on cross-sectional imaging in 47 of the 51 patients in this study. A

TABLE 3. Location of Lesions Identified by 111In-DTPA-Octreotide Scintigraphy, 68Ga-DOTATATE PET, and Cross-Sectional Imaging (CT ± MRI) in 47 Patients with Radiologic Evidence of Disease

Organ or region	111In-DTPA-octreotide scintigraphy	68Ga-DOTATATE PET	P*	CT ± MRI
Lung	3	9	0.001	16
Breast	0	1	NS	1
Pancreas	4	6	NS	6
Liver	6	23	<0.001	34
Gastrointestinal tract	0	7	<0.001	7
Kidney	2	3	NS	2
Spleen	0	0	NS	1
Pelvis or ovaries	2	1	NS	1
Thoracic nodes	0	17	<0.001	17
Mesenteric nodes	1	19	<0.001	37
Abdominal nodes	9	27	<0.001	45
Vertebrae	0	19	<0.001	23
Bones	0	36	<0.001	36
Total	27	168	<0.001	226

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*To determine whether a significant difference was present in number of lesions identified using 68Ga-DOTATATE PET and 111In-DTPA-octreotide scintigraphy, P > 0.05 was regarded as nonsignificant (NS).
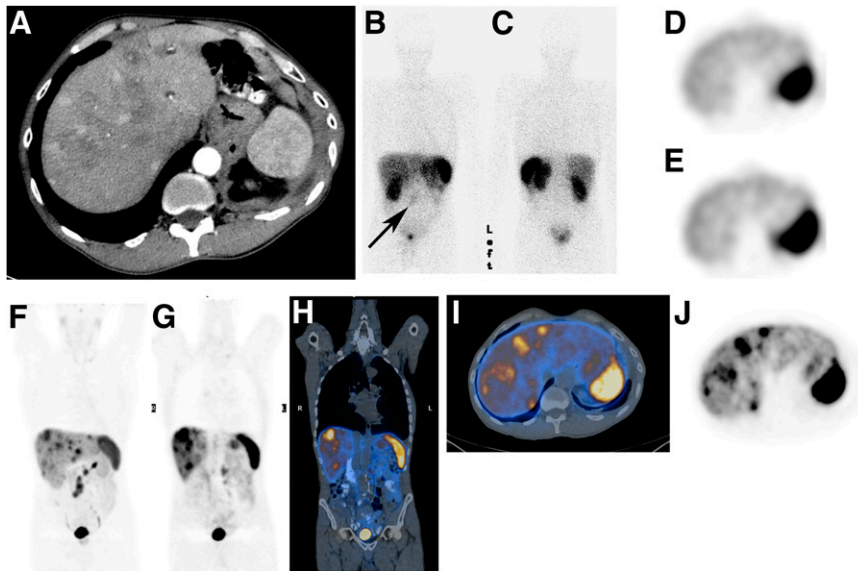
FIGURE 1. A 69-y-old man with low-grade metastatic midgut NET. (A) Arterial-phase CT shows multiple arterially enhancing and low-attenuation liver metastases. (B and C) Anterior and posterior whole-body ^{111}In-DTPA-octreotide scintigraphy shows low-grade (Krenning score, 1) mesenteric metastases (arrow) but no liver metastases. (D and E) Axial ^{111}In-DTPA-octreotide SPECT at level of spleen shows heterogeneous liver uptake with no discernable liver deposits. (F) Maximum-intensity-projection ^{68}Ga-DOTATATE PET shows multiple deposits in liver and mesentery. (G) Coronal ^{68}Ga-DOTATATE PET anterior to kidney shows multiple liver metastases. (H) ^{68}Ga-DOTATATE PET/CT of G. (I) Axial ^{68}Ga-DOTATATE PET/CT at level of spleen shows multiple liver metastases. (J) Axial ^{68}Ga-DOTATATE PET at level of spleen shows multiple liver metastases.

total of 226 lesions were identified with CT ± MRI, whereas ^{111}In-DTPA-octreotide scintigraphy identified 27 lesions and ^{68}Ga-DOTATATE PET identified 168 lesions. ^{68}Ga-DOTATATE PET identified 74.3% of all lesions—significantly more than were identified by ^{111}In-DTPA-octreotide scintigraphy ($P < 0.001$).

The locations of lesions (according to specific body region) identified by ^{68}Ga-DOTATATE PET and by ^{111}In-DTPA-octreotide scintigraphy were compared (Table 3). Because SPECT was performed only in the region of the chest and abdomen, skeletal metastases may not have been identified on planar imaging. Thirty-six bony lesions were identified by ^{68}Ga-DOTATATE PET and CT ± MRI, of which 28 were in the rib cage or pelvis. Eight bony metastases were identified in the long bones (limbs). The smallest lesion detected on ^{68}Ga-DOTATATE PET was a 6-mm node seen on CT.

^{68}Ga-DOTATATE PET and Histology. Histologic findings were available for all patients. Table 4 shows the number of positive cases in patients with different grades of disease. The results for ^{111}In-DTPA-octreotide are difficult to interpret in view of the patients selected. ^{68}Ga-DOTATATE PET showed good lesion recognition with low-grade tumors. The sensitivity of ^{68}Ga-DOTATATE PET decreased in the more aggressive and poorly differentiated tumors; however, this reduction did not reach significance.

Positive ^{68}Ga-DOTATATE Findings in Conjunction with Initially Negative CT Findings. In 2 cases, patients had undergone initial CT that had been reported as showing normal findings, though it is unclear whether bone windows were reviewed. One patient had normal biochemical markers and the other had raised chromogranin A levels. When these patients underwent ^{68}Ga-DOTATATE PET/CT, the PET portion identified multiple bony metastases; these

TABLE 4. Number of Positive ^{111}In-DTPA-Octreotide Scintigraphy and ^{68}Ga-DOTATATE PET Results in Patients with Different Histologic Grades of Disease

Histologic tumor grade	Total patients	Number of patients with disease on. . .			
		Cross-sectional imaging	^{111}In-DTPA-octreotide scintigraphy	^{68}Ga-DOTATATE PET	P*
Low	28	24	11 (45.8%)	22 (91.7%)	<0.001
Intermediate	19	19	3 (15.8%)	16 (84.2%)	<0.001
High	4	4	2 (50%)	3 (75%)	NS
Total	51	47	16	41	<0.001

*Comparison of number of patients with positive disease identified using ^{111}In-DTPA-octreotide scintigraphy and ^{68}Ga-DOTATATE PET for different histologic grades of tumor. $P > 0.05$ was regarded as nonsignificant (NS).

Positive for ^{111}In-DTPA-octreotide scintigraphy means weak or equivocal uptake (Krenning score < 2). Krenning score scale: 0 = no abnormality, 1 = faint uptake in tumor; 2 = clear uptake in tumor but less than in liver; 3 = uptake greater in tumor than in liver; 4 = accumulation much greater in tumor than in liver (18).

were found to correspond to sclerotic foci on CT when PET/CT images were reviewed.

Change in Clinical Management

To ascertain whether ^{68}Ga-DOTATATE PET altered the clinical management in patients who had already undergone ^{111}In-DTPA-octreotide scintigraphy, all case notes were reviewed. Changes in clinical management were classified as 1 of the following 4 categories: consideration of ^{90}Y-DOTATATE radiotargeted therapy; suitability for commencement of somatostatin analogs; an alteration of disease stage; and consideration of surgical resection, where this was deemed possible.

Among the 51 patients, management was altered in 36 (70.6%) after ^{68}Ga-DOTATATE PET. Of these 36, 20 were considered suitable for peptide receptor radiotargeted therapy with ^{90}Y-DOTATATE because of the strength of tracer uptake on ^{68}Ga-DOTATATE PET. A further 4 patients with negative results on both ^{68}Ga-DOTATATE and ^{111}In-DTPA-octreotide scanning were excluded from peptide receptor therapy with ^{90}Y-DOTATATE. In 7 patients without functional symptoms but positive for uptake on ^{68}Ga-DOTATATE PET, somatostatin analogs were commenced for their antiproliferative effects.

In 4 patients, surgery was regarded as a possible treatment option because of the presence of limited and resectable disease. In 3 patients, the disease was localized to the abdomen and pelvis, and in 1 patient, the disease was limited to the liver. In these patients, ^{68}Ga-DOTATATE PET changed clinical management by confirming that the disease shown on cross-sectional PET had not been identified on ^{111}In-DTPA-octreotide scintigraphy. Curative resections were performed in 2 patients, and there was no evidence of recurrence at 12 and 14 mo. Another patient underwent surgical debulking of more than 90% of the tumor load, and the remaining disease was stable at 6 mo after surgery. The fourth patient has, to date, been unwilling to undergo surgery and is considering other treatment options.

Finally, in 1 patient with no evidence of disease on CT or biochemically, low-grade uptake in the mediastinum and left lung was observed on the ^{111}In-DTPA-octreotide scan. ^{68}Ga-DOTATATE PET did not reveal any evidence of abnormal uptake, and the patient was regarded as disease-free. In this patient, ^{68}Ga-DOTATATE PET confirmed cross-sectional imaging findings but altered management by finding no evidence of the uptake that had been seen on ^{111}In-DTPA-octreotide scintigraphy.

DISCUSSION

To our knowledge, this study was the first to demonstrate that ^{68}Ga-DOTATATE PET can identify disease in patients with NETs when conventional ^{111}In-DTPA-octreotide findings are negative or show only faint uptake. Furthermore, ^{68}Ga-DOTATATE PET changed the clinical management of 70% of the patients studied.

Although ^{68}Ga-DOTATATE PET identified disease in patients with negative or weakly positive ^{111}In-DTPA-octreotide findings, it did not map the full extent of disease. ^{68}Ga-DOTATATE PET identified 74.3% of lesions documented by conventional cross-sectional imaging. There were individual cases in which some lesions were ^{68}Ga-DOTATATE–avid whereas others were not. These cases illustrate the variable SSTR expression and heterogeneity of NETs, especially with intermediate- and high-grade tumors.

Inherently, PET has spatial resolution superior to that of conventional SPECT. Reubi et al have demonstrated that ^{68}Ga-DOTATATE bound SSTR-2 and other SSTR subtypes with a considerably higher affinity than ^{111}In-DTPA-octreotide (21). The higher affinity of ^{68}Ga-DOTATATE for SSTR-2 may enable smaller lesions to be visualized on PET/CT. It is likely that whole-body SPECT would have identified more lesions, especially skeletal metastases, but whole-body SPECT is neither practical nor comfortable for patients. In areas where ^{111}In-DTPA-octreotide SPECT and ^{68}Ga-DOTATATE PET were performed, the number of lesions detected with PET was greater. It does not appear that lesion size is the only reason for increased lesion detection with ^{68}Ga-DOTATATE PET, compared with ^{111}In-DTPA-octreotide scintigraphy. As demonstrated in Figures 1 and 2, large lesions were identified on ^{68}Ga-DOTATATE PET and not on ^{111}In-DTPA-octreotide SPECT. The ^{111}In-DTPA-octreotide scintigraphy protocol used in this study requires a total scanning time of 50 min to 1 h, which for many patients is the most that can be tolerated. The SPECT protocol in this study is similar to that recommended in other guidelines (22). The speed of whole-body planar images in this study (7.2 cm/min) is faster than that recommended in the SNM guidelines, which suggest a speed of approximately 3 cm/min. The faster image acquisition used in this study may lead to some ^{111}In-DTPA-octreotide–avid lesions not being identified. A second limitation is the delay between ^{111}In-DTPA-octreotide scintigraphy and ^{68}Ga-DOTATATE PET (median time, 4 mo), since new lesions may have developed during the window between scans.

Studies using ^{68}Ga-DOTATOC PET have also shown higher sensitivity and specificity than ^{111}In-DTPA-octreotide scintigraphy (23). A study by Buchmann et al. on 27 patients demonstrated an increase in lesion identification with PET, compared with ^{111}In-DTPA-octreotide SPECT (13). Another study, by Gabriel et al., with a prospective design, compared ^{68}Ga-DOTATOC PET and ^{111}In-DTPA-octreotide SPECT in 84 patients and found that a significantly higher number of lesions were identified with ^{68}Ga-DOTATOC PET (14).

The purpose of our study was not to directly compare the performance of ^{111}In-DTPA-octreotide scintigraphy and ^{68}Ga-DOTATATE PET but to assess the clinical utility of ^{68}Ga-DOTATATE PET/CT in a specific subset with no uptake or low-grade uptake on ^{111}In-DTPA octreotide scintigraphy. In these patients, we have clearly demonstrated
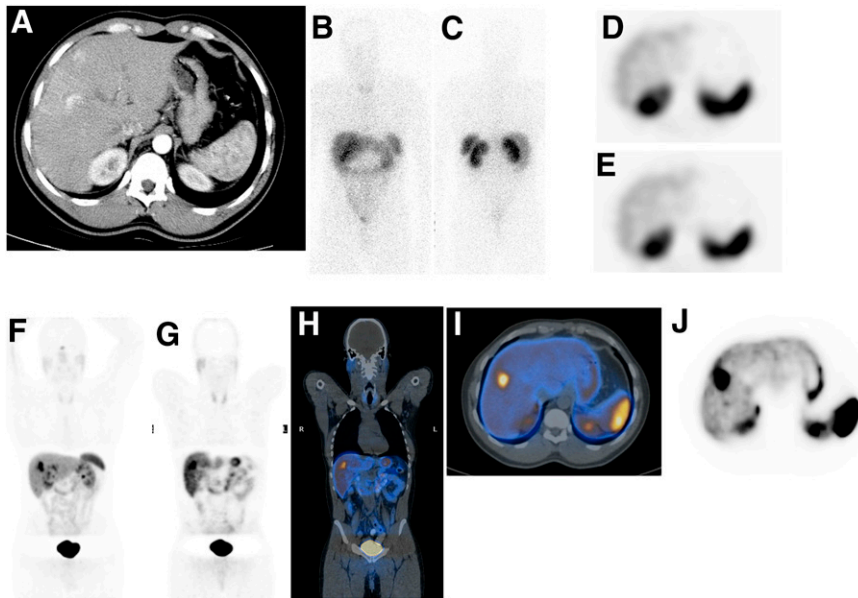
FIGURE 2. A 42-y-old man with intermediate-grade metastatic midgut NET. (A) Arterial-phase CT at level of splenic hilum shows 2 arterially enhancing liver metastases. (B and C) Anterior and posterior whole-body ^{111}In-DTPA-octreotide scintigraphy shows physiologic uptake only. (D and E) Axial ^{111}In-DTPA-octreotide SPECT at level of spleen shows no discernable liver lesions. (F) Maximum-intensity-projection ^{68}Ga-DOTATATE PET shows liver metastases. (G) Coronal ^{68}Ga-DOTATATE PET shows liver metastases. (H) ^{68}Ga-DOTATATE PET/CT of G. (I) Axial ^{68}Ga-DOTATATE PET/CT shows large metastatic liver deposit. (J) Axial ^{68}Ga-DOTATATE PET shows large metastatic liver deposit.

that ^{68}Ga-DOTATATE PET leads to changes in management. The role of ^{68}Ga-DOTATATE PET seems to be similar to that of ^{111}In-DTPA-octreotide scintigraphy, in that its main clinical uses are in localization of disease and assessment of suitability for treatment with somatostatin analogs and radiotargeted therapy.

In our study, 39% of patients were deemed suitable for radiotargeted therapy on the basis of ^{68}Ga-DOTATATE PET findings. No difference in response to peptide receptor therapy was observed between patients who were positive on ^{68}Ga-DOTATATE PET and negative on ^{111}In-DTPA-octreotide scintigraphy, compared with patients who received such therapy on the basis of positive ^{111}In-DTPA-octreotide findings. However, long-term follow-up data are required to confirm this finding.

There is evidence that somatostatin analogs have antitumor activity in patients with functional NETs (24). It is postulated that patients with nonfunctional NETs and negative ^{111}In-DTPA-octreotide scintigraphy findings but positive ^{68}Ga-DOTATATE PET findings may well benefit from somatostatin analog therapy.

At the time of primary staging, ^{68}Ga-DOTATATE PET has an important role in the localization of disease, especially in patients who are negative on ^{111}In-DTPA-octreotide imaging. From a surgical perspective, localization of the primary lesion, nodal involvement, and distant metastases is of the greatest importance. Our study has shown the clinical utility of ^{68}Ga-DOTATATE PET in this setting, in that it provides accurate staging of disease.

SSTR expression decreases as the histologic grade of tumor increases, and high-grade tumors have limited SSTR expression (25). In this study, ^{68}Ga-DOTATATE PET had similar sensitivities in identifying disease in low-, intermediate-, and high-grade tumors. For an accurate assessment of the role of ^{68}Ga-DOTATATE PET and ^{111}In-DTPA-

octreotide in patients with low-, intermediate- or high-grade tumors, a study looking at unselected NET patients would be of benefit to evaluate the sensitivity, specificity, and accuracy of this tracer. Within the literature, there is evidence that ^{68}Ga-DOTATATE PET is of limited value in patients with intermediate- and high-grade tumors and that ^{18}F-FDG PET may be more suitable in these cases (17).

Other PET tracers have also undergone trials for imaging of NETs, including ^{11}C-5-hydroxytryptophan and ^{18}F-fluoro-L-3,4-dihydroxyphenylalanine. These have shown promising results, with higher detection rates than those achieved with ^{111}In-DTPA-octreotide SPECT and CT (26). However, currently these substrates do not provide any therapeutic options, unlike somatostatin analogs, and therefore have limited clinical roles.

CONCLUSION

^{68}Ga-DOTATATE PET detects 74% of lesions in a selected group of patients with negative or faint uptake (Krenning score, <2) on ^{111}In-DTPA-octreotide scintigraphy and changes the clinical management in 70.6% of these patients

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