68Ga-DOTATATE PET/CT, 99mTc-HYNIC-Octreotide SPECT/CT, and Whole-Body MR Imaging in Detection of Neuroendocrine Tumors: A Prospective Trial

Elba Cristina Sá de Camargo Etchebehere[1], Allan de Oliveira Santos[1], Brenda Gumz[2], Andreia Vicente[1], Paulo Ghem Hoff[2], Gustavo Corradi[3], Wilson André Ichiki[1], José Geraldo de Almeida Filho[1], Saulo Cantoni[3], Edwaldo Eduardo Camargo[1], and Frederico Perego Costa[2]

[1]Division of Nuclear Medicine and PET/CT, Sirio Libanes Hospital, São Paulo, Brazil; [2]Oncology Center, Sirio Libanes Hospital, São Paulo, Brazil; and [3]Division of Radiology, Sirio Libanes Hospital, São Paulo, Brazil

There are different metabolic imaging methods, various tracers, and emerging anatomic modalities to stage neuroendocrine tumor (NET). We aimed to compare NET lesion detectability among 99mTc-hydrazinonicotinamide (HYNIC)-octreotide (somatostatin receptor scintigraphy [SSRS]) SPECT/CT, 68Ga-DOTATATE PET/CT, and whole-body diffusion-weighted MR imaging (WB DWI). **Methods:** Nineteen consecutive patients (34–77 y old; mean, 54.3 ± 10.4 y old; 10 men and 9 women) underwent SSRS SPECT/CT, 68Ga-DOTATATE PET/CT, and WB DWI. Images were acquired with a maximum interval of 3 mo between them and were analyzed with masking by separate teams. Planar whole-body imaging and SPECT/CT were performed from thorax to pelvis using a double-head 16-slice SPECT/CT scanner 4 h after injection of 111–185 MBq of 99mTc-HYNIC-octreotide. 68Ga-DOTATATE PET/CT was performed from head to feet using a 16-slice PET/CT scanner 45 min after injection of 185 MBq of tracer. WB DWI was performed in the coronal plane using a 1.5-T scanner and a body coil. The standard method of reference for evaluation of image performance was undertaken: consensus among investigators at the end of the study, clinical and imaging follow-up, and biopsy of suggestive lesions. **Results:** McNemar testing was applied to evaluate the detectability of lesions using 68Ga-DOTATATE PET/CT in comparison to SSRS SPECT/CT and WB DWI: a significant difference in detectability was noted for pancreas ($P = 0.0455$ and $P = 0.0455$, respectively), gastrointestinal tract ($P = 0.0455$ and $P = 0.0455$), and bones ($P = 0.0082$ and $P = 0.0082$). Two unknown primary lesions were identified solely by 68Ga-DOTATATE PET/CT. 68Ga-DOTATATE PET/CT, SSRS SPECT/CT, and WB DWI demonstrated, respectively, sensitivities of 0.96, 0.60, and 0.72; specificities of 0.97, 0.99, and 1.00; positive predictive values of 0.94, 0.96, and 1.00; negative predictive values of 0.98, 0.83, and 0.88; and accuracies of 0.97, 0.86, and 0.91. **Conclusion:** 68Ga PET/CT seems to be more sensitive for detection of well-differentiated NET lesions, especially for bone and unknown primary lesions. NET can be staged with 68Ga-DOTATATE PET/CT. WB DWI is an efficient new method with high accuracy and without ionizing radiation exposure. SSRS SPECT/CT should be used only when 68Ga-DOTATATE PET/CT and WB DWI are not available.

Neuroendocrine tumors (NETs) are slow-growing, rare endocrine malignancies with symptoms related to overproduction of bioactive substances or hormones in functioning tumors. However, in nonfunctioning tumors the diagnosis usually occurs at an advanced stage, rendering diagnosis of the primary lesion and detection of metastases difficult. Treatment and prognosis of NETs depend heavily on the stage and the originating organ (1).

Staging and restaging of NETs are performed by tumor marker measurements and by imaging studies to detect small lesions, such as CT of the chest, abdomen, and pelvis; MR imaging of the liver; and contrast-enhanced CT (2). However, these imaging modalities lack the specificity to diagnose malignant involvement (3) or to explain the nature and origin of the malignancy.

NETs are able to express 5 known subtypes of somatostatin receptor (4,5). More than 85% of gastrointestinal and pancreatic NETs have a high affinity for somatostatin receptors 2, 3, and 5 and also bind to octreotide (6,7).

Radiolabeled γ-emitting somatostatin analogs can detect somatostatin receptor–expressing NETs with 67%–100% sensitivity, superior to conventional imaging (8). Although somatostatin receptor scintigraphy (SSRS) is highly efficient for whole-body imaging, detection of lesions is difficult in organs with intense physiologic uptake, with low receptor density, or small size (9). Additionally, the physical characteristics of 111In do not make it an ideal tracer for imaging. On the other hand, the development of technetium-labeled tracers such as 99mTc-hydrazinonicotinamide (HYNIC)-octreotide and others has overcome the limitations of 111In for scintigraphic imaging. In addition, hybrid SPECT/CT has higher accuracy and specificity for lesion detection. Therefore, the use of SPECT/CT with SSRS labeled with 99mTc combines state-of-the-art scintigraphic imaging using the ideal γ-emitting isotope with structural CT information.

PET has a higher spatial resolution than scintigraphy (3–6 mm vs. 10–15 mm, respectively). 68Ga-DOTATATE PET/CT is more efficient than SSRS for evaluating small NET lesions. Additionally, the affinity of 68Ga-DOTATATE for binding to somatostatin receptor 2 is higher than that of 111In-octreotide ($2.5 ± 0.5$ nM vs. $22 ± 3.6$ nM)

(10,11). ^{68}Ga-DOTATATE PET/CT combines state-of-the-art PET imaging with an ideal positron-emitting isotope.

Whole-body diffusion-weighted MR imaging (WB DWI) has recently emerged as a tool for detection of metastasis without intravenous contrast material or radiation exposure that may possibly detect NET lesions in the entire body in a single acquisition. Only a few studies have addressed the value and practicality of WB DWI in staging NETs. The purpose of this study was to compare the detectability of NET lesions among 3 state-of-the-art imaging modalities—SPECT/CT with radiolabeled peptides, PET/CT with radiolabeled peptides, and WB DWI—and to establish the most appropriate work-up for the patient.

MATERIALS AND METHODS

The institutional review board and ethics committee approved this cross-sectional study (no. 2013/283.777). All patients gave written informed consent.

To be included, patients had to be older than 18 y, have a histologic diagnosis of NET, have suspected tumor recurrence, have no prior history of other malignant primary neoplasms, be nonlactating and nonpregnant, sign the informed consent form, undergo all imaging studies within an interval of no more than 3 mo, and receive no intervention or treatment during the imaging period.

Nineteen consecutive patients who met the inclusion criteria underwent staging with SSRS SPECT/CT, ^{68}Ga-DOTATATE PET/CT, and WB DWI. Three teams of experienced physicians analyzed the images separately and were masked to the results of the other imaging procedures. In cases of disagreement between 2 physicians, the third expert would be used to reach a consensus.

Patient age ranged from 34 to 77 y (mean ± SD, 54.3 ± 10.4 y); 10 were men and 9 women. Three patients had cancer of unknown primary site. The primary malignancies included tumors of the bronchi ($n = 4$), pancreas ($n = 6$), and gut ($n = 6$). Tumor markers included Ki-67 ranging from 1% to 26% (mean, 9.5% ± 8.4%) and chromogranin A ranging from 1.6 to 901 ng/mL (mean, 151.5 ± 290.9 ng/mL). The mean

TABLE 1
Lesion Detection Capability of SSRS SPECT/CT, ^{68}Ga PET/CT, and WB DWI

Variable	N/P	P value ^{68}Ga-DOTATATE PET/CT vs. SSRS SPECT/CT	^{68}Ga-DOTATATE PET/CT vs. WB DWI
All solid organs	N	0.0253	0.0833
	P		
Lungs and pleura	N	1.0000	0.1573
	P		
Liver	N	0.1573	0.3173
	P		
Pancreas	N	0.0455	0.0455
	P		
Gastrointestinal tract	N	0.0455	0.0455
	P		
All LNs	N	0.5637	1.0000
	P		
Cervical LNs	N	1.0000	1.0000
	P		
Thoracic LNs	N	0.5637	0.0833
	P		
Abdomen and pelvic LNs	N	0.3137	0.3173
	P		
All skeletal system	N	0.0082	0.0082
	P		
Bones of spine and pelvis	N	0.0143	0.0455
	P		
Thoracic bones	N	0.0143	0.0143
	P		
Bones of limbs	N	0.0253	
	P		0.0455
Skull and skull base	N	0.0455	
	P		0.0455

LNs = lymph nodes; N = negative; P = positive.

interval to perform the 3 studies was 21.8 ± 33.5 d (range, 1–93 d), with a mean clinical follow-up of 4 mo.

SSRS SPECT/CT and ^{68}Ga-DOTATATE PET/CT were scheduled 4 wk after the last treatment with long-acting octreotide (Sandostatin; Novartis) or 24 h after treatment with short-acting analogs.

SSRS SPECT/CT

Images were obtained using a double-head SPECT/CT 16-slice camera (Symbia; Siemens Healthcare Solutions) with low-energy parallel-hole collimators.

Patients were injected with 111–185 MBq (3–5 mCi) of ^{99m}Tc-HYNIC-octreotide (RPH). Windows were set at 140 keV, a 10 cm/min scan rate was used, and a 195-cm extent was used for acquisition of planar whole-body images. Thoracic, abdominal, and pelvic SPECT/CT images were obtained after 4 h using a 128 × 128 matrix and 40 s/projection. Images were reconstructed iteratively. CT images were acquired with 130 kV, 15 mAs, a 0.8-s rotation speed, and a 5-mm slice thickness. Appendicular and skull SPECT/CT images were obtained only when suggestive lesions were noted on the planar whole-body images.

^{68}Ga-DOTATATE PET/CT

Images were acquired using a 16-slice PET/CT scanner (Biograph, True V; Siemens Healthcare Solutions). The acquisition began 45 min after injection of 185 MBq (5 mCi) of ^{68}Ga-DOTATATE (IPEN). Images were acquired from the proximal third of the thigh to the head (~6–7 bed positions) at 5 min/bed position. Images were reconstructed iteratively. CT images were acquired with 130 kV, 15 mAs, a 0.8-s rotation speed, and a 2-mm slice thickness.

WB DWI

MR imaging was performed with a 1.5-T whole-body imager. Coronal whole-body images (head to thigh) were obtained using a body coil. Diffusion-weighted, T1-weighted, and short-τ inversion recovery sequences were obtained, and for each, at least 5 continuous stations covering the whole body were acquired. Diffusion encoding was performed in one direction.

Lesions Detected

SSRS SPECT/CT and ^{68}Ga-DOTATATE PET/CT findings were designated as positive when intense focal uptake in comparison to the adjacent tissues was seen in the coronal, transaxial, and sagittal views. Linear and tubular areas of increased uptake in the intestinal tract were described as physiologic and as negative for malignancy.

Lesions seen on WB DWI were analyzed in terms of number, size, location, and signal intensity and were compared with the T1-weighted and short-τ inversion recovery sequences to rule out false-positive findings. Lymph nodes were defined as malignant according to the diameter of the small axis.

In all 3 studies, lesion location was categorized into 3 main regions: organs, lymph nodes, and musculoskeletal system. Organs were further subdivided into lungs/pleura, liver, pancreas, adrenals, and gastrointestinal tract. Lymph nodes were further subdivided into cervical, thoracic (mediastinal, axillary, and clavicular), and abdominal/pelvic. The musculoskeletal system was further subdivided into spine, thorax (clavicles, ribs, sternum, and scapulae), limbs, skull, and soft tissues. The number of lesions that could clearly be identified as a sole focus was determined by each method in the 15 regions studied.

Confluent or irregular liver lesions were considered as a single lesion. All regions analyzed were considered either negative or positive. In the liver, lymph nodes, and bones, the number of lesions was counted.

Standard Method of Reference

The performance of the 3 imaging methods was evaluated using the following criteria: consensus among investigators at the end of the study evaluating all lesions by all methods, clinical follow-up, and biopsy of suggestive lesions when possible.

Statistical Analysis

Frequency and percentage were calculated for the qualitative variables, and mean, SD, median, minimum and maximum values, and number of valid observations were calculated for the quantitative variables.

McNemar testing was used to compare the qualitative variables of lesion detectability. The nonparametric Wilcoxon test was applied for paired samples of quantitative variables. The level of significance was set at 5% ($P \leq 0.05$).

The sensitivity, specificity, positive and negative predictive values, and accuracy of the 3 imaging modalities were calculated, and the equivalence test was applied to evaluate the difference in performance among the three. The maximum difference in equivalence was set at 0.15 (15%), and the level of significance was set at 5% ($P \leq 0.05$).

RESULTS

When ^{68}Ga-DOTATATE PET/CT was compared with SSRS SPECT/CT and WB DWI, the former detected more lesions in the pancreas ($P = 0.0455$ and $P = 0.0455$; McNemar test) and gastrointestinal tract ($P = 0.0455$ and $P = 0.0455$; McNemar test) (Table 1). ^{68}Ga-DOTATATE PET/CT was the only imaging modality to detect 2 unknown primary lesions and a metastasis in the gastrointestinal tract (Fig. 1). However a false-positive case of marked uptake occurred in the uncinate process.

When ^{68}Ga-DOTATATE PET/CT was compared with SSRS SPECT/CT and WB DWI, all were similar for lung ($P = 1.000$ and $P = 0.1573$; McNemar test) and liver lesions ($P = 0.1573$ and $P = 0.3173$; McNemar test). Lung nodules close to the liver dome were false-negative on ^{68}Ga-DOTATATE PET/CT and SSRS SPECT/CT but not on WB DWI (Fig. 2).

One liver metastasis was not detected by WB DWI after chemotherapy but was positive on ^{68}Ga-DOTATATE PET/CT and SSRS SPECT/CT, showing lack of complete response to treatment (Fig. 3). Subcentimeter hepatic metastases were easily identified on ^{68}Ga-DOTATATE PET/CT but were detected only retrospectively on dedicated MR imaging of the liver (Fig. 4).

When ^{68}Ga-DOTATATE PET/CT was compared with SSRS SPECT/CT and WB DWI, all three were similar for detection of lymph node lesions in the neck ($P = 1.000$ and $P = 1.000$; McNemar test), thorax ($P = 0.5637$ and $P = 0.0833$; McNemar test), and abdomen and pelvis ($P = 0.3137$ and $P = 0.3137$; McNemar
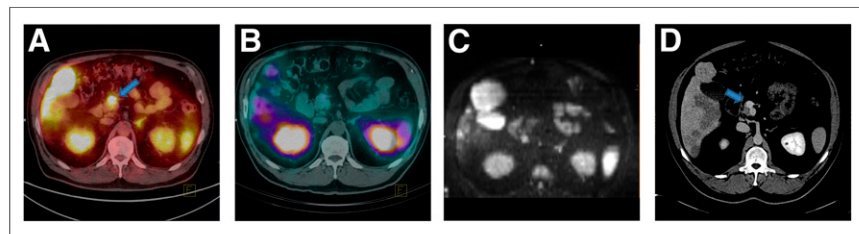

FIGURE 1. A 49-y-old man with NET of unknown origin for over 4 y. ^{68}Ga-DOTATATE PET/CT (A) identified primary pancreatic lesion (arrow), whereas SSRS SPECT/CT (B) and WB DWI (C) did not. This lesion was noted only retrospectively (arrow) on dedicated abdominal CT (D) performed 4 y previously.
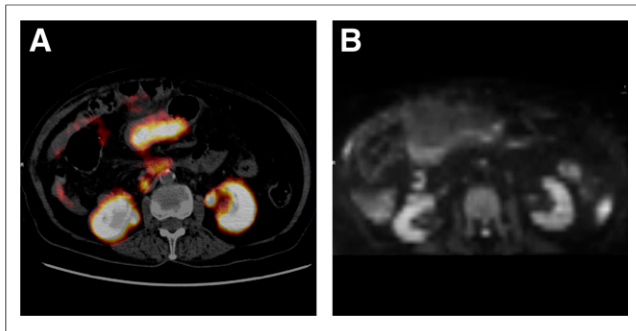
FIGURE 2. A 77-y-old woman with NET of unknown origin. ^{68}Ga-DOTATATE PET/CT (A) showed multiple liver metastases and mesenteric nodule, whereas WB DWI (B) did not identify mesenteric nodule.

test) (Fig. 5). One enlarged hepatogastric lymph node detected on WB DWI was false-negative on ^{68}Ga PET/CT and SSRS SPECT/CT.

^{68}Ga-DOTATATE PET/CT detected more bone metastases overall than did SSRS SPECT/CT and WB DWI ($P = 0.0082$ and $P = 0.0082$; McNemar test). False-negative findings occurred with WB DWI in a wide variety of small bone lesions (Fig. 5). ^{68}Ga-DOTATATE PET/CT had a higher detection rate in pelvic bones ($P = 0.0143$ and $P = 0.0455$; paired Wilcoxon test), thoracic bones ($P = 0.0143$ and $P = 0.0143$; McNemar test), the appendicular skeleton ($P = 0.0253$ and $P = 0.0455$; McNemar test), and the base of the skull ($P = 0.0455$ and $P = 0.0455$; McNemar test).

^{68}Ga-DOTATATE PET/CT and WB DWI performed equally in detecting solid organ lesions overall ($P = 0.0833$; McNemar test) and were better than SSRS SPECT/CT ($P = 0.0253$; McNemar test). The sensitivity, specificity, positive and negative predictive values, and accuracy for overall lesion detection for each imaging modality are listed in Table 2.

DISCUSSION

To our knowledge, this was the first study to evaluate state-of-the-art whole-body diagnostic imaging modalities (SPECT/CT, PET/CT, and WB DWI) in NET tumors. On the basis of our data, a diagnostic algorithm may be recommended to develop the best strategy for management of NETs.

SSRS labeled with ^{111}In has been considered the gold standard for the staging of well- and moderately differentiated NETs, by specifically binding to somatostatin receptors 2, 3, and 5, although there is the disadvantage of lack of availability and high cost. ^{99m}Tc-HYNIC-octreotide is widely available and has a low cost, high specificity, high receptor affinity, low radiation exposure, less delay in acquisition time, and high imaging quality, especially with the current use of SPECT/CT. The uptake of the two tracers is comparable (*12*). Because of these characteristics, we chose to evaluate these patients with this modality, thus reducing radiation exposure and scanning time and increasing the accuracy and sensitivity of lesion detection. SSRS SPECT/CT, by determining the precise location of lesions and reducing false-positive results, has been shown to be superior to SSRS SPECT, altering clinical management in 26% of patients (*13*).

Many PET/CT peptide tracers could have been used in this study, such as DOTANOC, DOTALAN, DOTATOC, and even DOPA (although the latter has a different uptake mechanism and kinetics), since there are no definitive data suggesting the superiority of DOTATATE over the others. ^{68}Ga-DOTALAN and ^{68}Ga-DOTATATE have similar kinetics, and the latter has shown superiority in lesion detection due to higher uptake (*14*). We performed the studies with ^{68}Ga-DOTATATE because it is the only PET peptide tracer available in our country.

^{68}Ga-DOTATATE PET/CT is more convenient for the patient and referring physician than SSRS SPECT/CT. The entire PET/CT procedure can be performed in approximately 2 h (in contrast to 4 h), image acquisition is approximately 20 min (in contrast to 1.5 h), and the labeling can be accomplished with an in-house generator and with costs similar to the SSRS SPECT/CT procedure. The main disadvantage of SSRS and ^{68}Ga-DOTATATE PET/CT is the use of ionizing radiation.

MR imaging takes advantage of the highly vascular nature of NETs; with intravenous contrast material, lesions enhance intensely during the arterial phase and wash out during the delayed phase. On the other hand, since NETs significantly reduce water diffusion compared with normal tissues, in WB DWI the tumor displays a high signal intensity. We previously reported the potential of this novel patient-friendly tool that does not require intravenous contrast material, does not use ionizing radiation, and can be correlated with other T1- and T2-weighted MR imaging acquisitions for better tumor location and characterization (*15*). WB DWI has a fast acquisition phase and can easily be used as a roadmap to identify small and large NET lesions. Imaging can also be repeated to assess tumor response with morphologic and functional information. WB DWI requires movable table platforms, which are not yet commercially available from all manufacturers. Despite the relatively high cost at the moment, the precise anatomic information and lack of venous contrast material make WB DWI an attractive method that should be further investigated.

All 3 studies performed equally well for detection of lung nodules. However, WB DWI was less sensitive than CT because subcentimeter nodules, although clearly seen on CT, were difficult to detect on coronal WB DWI. Both ^{68}Ga-DOTATATE PET/CT and SSRS SPECT/CT were considered negative if there was no uptake in the lung nodules, even though they were clearly identified and reported as suggestive of metastases because of the CT portion of the studies. Some patients presented marked uptake in subcentimeter nodules. False-negative lung
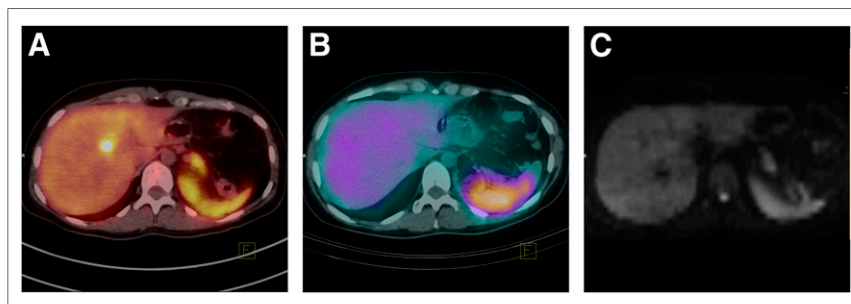

FIGURE 3. A 34-y-old woman with bronchial NET who underwent all 3 studies to evaluate response after chemotherapy. Patient had multiple liver lesions with marked uptake before chemotherapy. After chemotherapy, ^{68}Ga-DOTATATE PET/CT (A) demonstrated marked uptake in one remaining liver metastasis, indicating lack of complete response to treatment, whereas SSRS SPECT/CT (B) and WB DWI (C) did not identify this lesion.
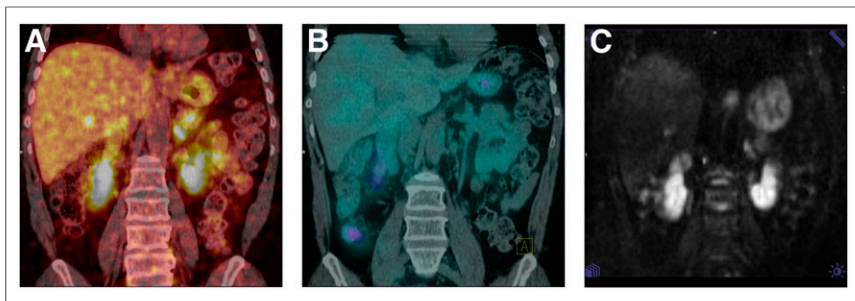
FIGURE 4. A 61-y-old woman with ileum NET. ^{68}Ga-DOTATATE PET/CT (A) easily identified sub-centimeter hepatic metastases, whereas SSRS SPECT/CT (B) and WB DWI (C) did not detect these lesions.

nodules on ^{68}Ga-DOTATATE PET/CT and SSRS SPECT/CT occurred in lesions close to the liver dome because of the respiratory motion artifact. Respiratory gating, which was not available at the time of this study, is an important tool to avoid mistakes at the level of diaphragmatic lesions.

Prior studies have stated that there are limitations in the detection of hepatic metastases using ^{68}Ga-DOTATATE PET whereas contrast-enhanced CT and MR imaging seem more valuable in this setting (16). This may have been due to the quality of PET and SPECT equipment in prior studies, since they were not hybrid modalities. In contrast, our study showed that liver metastases were equally and reliably seen with ^{68}Ga-DOTATATE PET/CT and WB DWI and that both were superior to SSRS SPECT/CT. Published data have suggested that the detectability of NET liver metastases on MR imaging is equal to that on ^{18}F-FDG PET/CT (17). This also seems to be the case for ^{68}Ga-DOTATATE PET/CT studies. In our study, subcentimeter hepatic metastases with standardized uptake values in the range of 40–90 (and therefore above the spatial resolution of the equipment) were clearly seen on ^{68}Ga-DOTATATE PET/CT and were only retrospectively detected by dedicated liver MR imaging.

Detection of lymph nodes was virtually the same for both ^{68}Ga-DOTATATE PET/CT and WB DWI. Separating by site, ^{68}Ga-DOTATATE PET/CT detected slightly more thoracic nodes than WB DWI. The latter lacks sensitivity in detecting mediastinal nodes near the heart. In one patient, WB DWI detected an enlarged hepatogastric lymph node that did not take up ^{68}Ga-DOTATATE, possibly because the patient's disease was rapidly progressing and was dis-
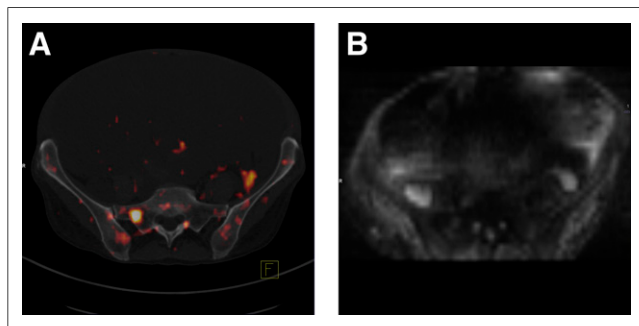
seminated, and this lesion possibly had become undifferentiated. The patient died within 7 mo.

The detection of adrenal lesions on ^{68}Ga-DOTATATE PET/CT studies is challenging because of the marked physiologic uptake in this organ. However, there was no difference in detection of lesions in the adrenal gland when all 3 imaging modalities were compared.

On the other hand, although there is physiologic uptake in the gastrointestinal tract, ^{68}Ga-DOTATATE PET/CT detected significantly more lesions than WB DWI and SSRS SPECT/CT. One unknown primary in the duodenum (undetected for years), one gastrointestinal tract metastasis, and other new lesions were detected only with ^{68}Ga-DOTATATE PET/CT.

A striking finding was the capability of ^{68}Ga-DOTATATE PET/CT to detect pancreatic lesions. Physiologic uptake in the uncinate process with DOTATOC and DOTANOC has previously been described (18,19). Marked ^{68}Ga-DOTATATE uptake in the uncinate process, which could be due to a higher cellular somatostatin receptor concentration, led to a false-positive study, and to our knowledge, this phenomenon with this tracer has not previously been described. In contrast, a patient with an unknown primary for years presented with marked focal ^{68}Ga-DOTATATE uptake. Retrospective analysis of the dedicated CT scan demonstrated a 0.4-cm lesion, which is in accordance with the theory that subcentimeter lesions, even when below the spatial resolution of the equipment, may be detected because of the markedly high ^{68}Ga-DOTATATE uptake. In addition, as seen in prior reports (20), there was a significant difference in lesion detectability in the pancreas between ^{68}Ga-DOTATATE PET/CT and WB DWI or SSRS SPECT/CT.

The most significant difference in lesion detection was clearly in the skeletal system, regardless of lesion size. Prior studies have shown higher detection rates of bone lesions with ^{68}Ga-peptides (on dedicated PET) than with ^{111}In-octreotide-SSRS and CT (2,21). In our study, ^{68}Ga-DOTATATE PET/CT detected more bone lesions overall and also by site (skull/skull base, thoracic bones, spine/pelvis, and bones of the limbs) than did WB DWI or SSRS SPECT/CT. On retrospective analysis, these strikingly small lesions detected by ^{68}Ga-DOTATATE PET/CT were identified on WB DWI but not on SSRS SPECT/CT. WB DWI had difficulty in detecting lesions in the rib cage and scapulae (because of the width of these bones), skull and skull base (because of the high signal intensity from the brain), sacrum, and ischium. A 6-mm sacral lesion was detected exclusively on ^{68}Ga-DOTATATE PET/CT and was retrospectively confirmed by dedicated MR imaging. Bone lesions in the femur were detected only on ^{68}Ga-DOTATATE PET/CT. Additional changes in the therapeutic strategy and prognostic information occurred in our patient population because bone metastases require more aggressive treatment.

An interesting finding was that when the ^{68}Ga-DOTATATE PET/CT scan was repeated in some patients (for reevaluation of equivocal findings), an increase in uptake was noted. These patients were asked to discontinue somatostatin analogs for a longer time, which may have increased the sensitivity of the study, revealing equivocal lesions. In one patient, the standardized uptake value of lesions almost doubled and new lesions were identified. Although this finding may have been due to progression

FIGURE 5. A 58-y-old woman with pancreatic NET. A 6-mm sacral metastasis was detected exclusively by ^{68}Ga-DOTATATE PET/CT (A) and was confirmed retrospectively by dedicated MR imaging; WB DWI (B) did not detect this lesion.

TABLE 2
Performance of SSRS SPECT/CT, ^{68}Ga-DOTATATE PET/CT, and WB DWI According to Sites

| Organ type | Imaging modality | Percentage | | | | |
		Sensitivity	Specificity	PPV	NPV	Accuracy
Overall	SSRS SPECT/CT	0.60	0.99	0.96	0.83	0.86
	^{68}Ga-DOTATATE PET/CT	0.96	0.97	0.94	0.98	0.97
	WB DWI	0.72	1.00	1.00	0.88	0.91
All solid organs	SSRS SPECT/CT	0.75	1.00	1.00	0.43	0.79
	^{68}Ga-DOTATATE PET/CT	1.00	0.67	0.94	1.00	0.95
	WB DWI	0.88	1.00	1.00	0.60	0.89
Lung and pleura	SSRS SPECT/CT	0.50	1.00	1.00	0.88	0.89
	^{68}Ga-DOTATATE PET/CT	0.50	1.00	1.00	0.88	0.89
	WB DWI	1.00	1.00	1.00	1.00	1.00
Liver	SSRS SPECT/CT	0.85	1.00	1.00	0.75	0.89
	^{68}Ga-DOTATATE PET/CT	1.00	1.00	1.00	1.00	1.00
	WB DWI	0.92	1.00	1.00	0.86	0.95
Pancreas	SSRS SPECT/CT	0.75	1.00	1.00	0.94	0.95
	^{68}Ga-DOTATATE PET/CT	1.00	0.80	0.57	1.00	0.84
	WB DWI	0.75	1.00	1.00	0.94	0.95
Gastrointestinal tract	SSRS SPECT/CT	0.50	1.00	1.00	0.94	0.95
	^{68}Ga-DOTATATE PET/CT	1.00	0.82	0.40	1.00	0.84
	WB DWI	0.50	1.00	1.00	0.94	0.95
Lymph nodes	SSRS SPECT/CT	0.85	1.00	1.00	0.75	0.89
	^{68}Ga-DOTATATE PET/CT	0.92	1.00	1.00	0.86	0.95
	WB DWI	1.00	1.00	1.00	1.00	1.00
Musculoskeletal system	SSRS SPECT/CT	0.46	1.00	1.00	0.46	0.63
	^{68}Ga-DOTATATE PET/CT	1.00	1.00	1.00	1.00	1.00
	WB DWI	0.42	1.00	1.00	0.50	0.63

NPV = negative predictive value; PPV = positive predictive value.

of the disease, the time between the studies (<3 mo) in a slow-growing tumor makes this possibility less likely.

The oncologist's choice of image modality will ultimately be based on several factors, including local availability, cost, and insurance coverage. An interesting algorithm would be to perform ^{68}Ga-DOTATATE PET/CT on initial staging since it is superior to SSRS SPECT/CT, ^{18}F-FDG PET/CT, and WB DWI in the detection of NETs (10). ^{68}Ga-DOTATATE PET/CT has a higher ability to detect unknown primary tumors, serving as a baseline study before initiation of therapy, a way to evaluate the possibility of SSRS therapy, and a prognostic marker (22). In addition, a study performed on 4,210 NET patients using ^{68}Ga-DOTATATE PET/CT was able to detect rare metastases (myocardium, breast, retro-orbital region, uterus, skin, brain, spleen, testes, seminal vesicle, and muscles) not detected by other methods (23).

Other groups have suggested that SSRS SPECT alone should be used for NET staging when ^{68}Ga-DOTATATE PET/CT is not available (24). We have shown that even when SPECT/CT is performed and compared with ^{68}Ga PET/CT, the latter is superior. Therefore, ^{68}Ga-DOTATATE PET/CT should be recommended as a first-line tool for whole-body NET staging.

On the other hand, WB DWI is a method that does not use radiation. Although WB DWI scanning requires approximately 40 min, which is a disadvantage and costly, WB DWI may be used as a follow-up tool. However, it is not known if maintenance of somatostatin analog medication during WB DWI could reduce its accuracy. Furthermore, a differential diagnosis of lesions seen on WB DWI is warranted since these lesions may become undifferentiated and not respond to therapy. We believe that the evaluation of tumor response by WB DWI should be prospectively evaluated further. Therefore, ^{68}Ga-DOTATATE PET/CT can also be recommended for patient follow-up when WB DWI findings are equivocal and for evaluation of treatment.

CONCLUSION

Different state-of-the-art imaging modalities can be used to evaluate NETs. ^{68}Ga-DOTATATE PET/CT seems to be more sensitive for detection of NET lesions. We propose a diagnostic algorithm that starts with staging of the patient with ^{68}Ga-DOTATATE PET/CT. Follow-up studies may be undertaken using either ^{68}Ga-DOTATATE PET/CT or WB DWI, although with the latter, the lack of radiation may be insufficient justification for its use in this setting and it is still unclear if there is enough accuracy to evaluate therapy. SSRS SPECT/CT should be used when ^{68}Ga-DOTATATE PET/CT is not available. A larger number of patients are necessary to

confirm our findings and to evaluate the impact on patient management and the cost-effectiveness of this algorithm.

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