Cerrahpaşa Med J 2023; 47(1): 7-13 ORIGINAL ARTICLE

Comparison of Whole-Body Ga-68 DOTA TATE Positron Emission Tomography and Magnetic Resonance Imaging in the Detection of Bone Metastasis of Neuroendocrine Tumor in Simultaneous 3T Positron Emission Tomography/Computed Tomography

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Abstract

Objective: Neuroendocrine tumors are rare neoplasms that often arise from neuroendocrine cells in gastro-entero-pancreatic and bronchopulmonary tissues. Bone metastases are observed less frequently than liver metastases. In current oncological practice, Ga-68 DOTA-labeled peptide positron emission tomography/computed tomography is performed in neuroendocrine tumor patients. Thanks to positron emission tomography/magnetic resonance imaging devices developed in recent years, it has become possible to obtain positron emission tomography images and magnetic resonance imaging sequences. This study aimed to compare the diagnostic efficiency between Ga-68 DOTA TATE positron emission tomography and magnetic resonance imaging components in detecting bone metastases in patients with neuroendocrine tumor undergoing Ga-68 DOTA TATE positron emission tomography/magnetic resonance imaging.

Methods: This study included 63 patients with neuroendocrine tumor who underwent Ga-68 DOTA TATE positron emission tomography/magnetic resonance imaging screening. First, positron emission tomography images and magnetic resonance imaging sequences were evaluated separately to detect bone metastases. Afterward, both the components were assessed together, and their contribution was investigated according to positron emission tomography images alone.

Results: Patient-based sensitivity, specificity, positive predictive value, negative predictive value, and accuracy analysis for bone metastasis were 0.96, 0.87, 0.82, 0.97, and 0.90 for positron emission tomography and 0.71, 0.87, 0.77, 0.82, and 0.80 for magnetic resonance imaging, respectively. Diffusion-weighted imaging and short-tau inversion recovery sequences do not seem to provide any additional benefit to the clinical approach.

Conclusion: Ga-68 DOTA TATE positron emission tomography/magnetic resonance imaging evaluated bone lesions in neuroendocrine tumor patients with high sensitivity but low specificity. Our study shows that diffusion-weighted imaging and short-tau inversion recovery sequences do not contribute to the clinical approach and lead to ambiguous results. It is thought that removing these sequences from the protocol will increase patient compliance, and prospective studies involving large patient groups are needed.

Keywords: PET/MRI, Ga-68 DOTA TATE, neuroendocrine tumors, bone metastasis

Introduction

Neuroendocrine tumors (NETs) are rare neoplasms that frequently originate from gastro-entero-pancreatic (GEP) and bronchopulmonary tissues consisting of neuroendocrine cells.[1] Although it is a slowly progressing tumor, liver metastases can be seen in most patients even at diagnosis.[2] Bone metastases are less common than liver metastases.[3] A recent meta-analysis reported that 18% of patients had bone metastases.[4] It is frequently detected in the pelvic bones and columna vertebralis.[5,6]

No correlation was found between the location of the primary tumor and the tumor grade in developing bone metastasis in NET patients.[7] When bone metastasis occurs in NET, it is primarily asymptomatic and usually found incidentally in conventional or nuclear medicine imaging.[8]

Studies reported that bone metastases were associated with poor prognosis in NET patients.[9,10] However, a recent meta-analysis showed that patients with bone metastases had shorter overall survival than patients without bone metastases.[4] On the other hand, another study suggested that this patient group still had a relatively long survival.[11]

Positron emission tomography/computed tomography (PET/CT) imaging with Ga-68 DOTA-labeled peptides can show somatostatin receptor overexpression in the NETs and their metastasis and,

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therefore, detects bone metastases with higher sensitivity than CT and bone scintigraphy.[12,13] Whole-body (WB) magnetic resonance imaging (MRI) is another modality used to evaluate bone metastases in patients with NET. However, WB MRI shows lower sensitivity in detecting bone metastases than Ga-68 DOTA-labeled peptide PET/CT.[14,15]

Thanks to PET/MR devices developed in recent years, it has become possible to obtain PET images and MRI sequences simultaneously. The diversity of sequences in MRI and low radiation exposure are potential advantages of this device. However, patient compliance is more difficult due to the narrower PET/MR gantry and longer imaging duration than PET/CT. For these reasons, oncology patients prefer PET/CT over PET/MR.[16] Reducing routine imaging time may increase the preferability of PET/MR. For this reason, MRI sequences acquired for the WB need to be modified, mainly when it is adjunctive to PET imaging using specific radiopharmaceuticals.

This study aimed to compare the diagnostic efficiency between Ga-68 DOTA TATE PET (TATE) and magnetic resonance imaging (MRI) components in detecting bone metastases in patients with NET who underwent WB Ga-68 DOTA TATE PET/MRI. In addition, we aimed to investigate if there is any added value in the evaluation of PET and MR components compared to the assessment performed with PET alone in detecting bone metastases.

Material and Method

The study was approved by the Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine Institutional Ethics Committee for Clinical Research (08/18/2021-178293). The study was conducted between July 2017 and December 2020. All participants signed an informed consent form.

Patient Population

This study included 63 patients with NET who underwent Ga-68 DOTA TATE PET/MR screening for staging, restaging, and evaluation of response to treatment. Inclusion and exclusion criteria are shown in Table 1.

In total, 25 (39.6%) women and 38 (60.4%) men participated in the study; the mean age was 55 ± 11.8 (range 29-81) years. Forty-six had GEP origin, 7 had lung origin, 7 had NET of unknown primary, and 3 had other sources (thyroid, thymus, and prostate).

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
• Having operation or pathologically proven diagnosis of neuroendocrine tumor
• Having at least 1 Ga-68 DOTA TATE PET imaging before or after index Ga-68 DOTA TATE PET/MRI
Exclusion Criteria
• <18 years of age
• Pregnancy
• Having material incompatible with MRI
• Intolerance to lying in MRI
• Claustrophobia
• Missing data

MRI, magnetic resonance imaging; PET, positron emission tomography

Table 2. Patient Characteristics

	All Patients
N	63
Sex (female/male)	25/38
Mean age (years)	55 ± 11.8
Tumor grade	
Grade 1	16
Grade 2	22
Grade 3	2
Unknown	23
The primary site of disease	
GEP-NET	46 (73%)
Lung	7 (11%)
Other	3 (5%)
Unknown	7 (11%)
PET/MRI indications	
Staging	2 (3%)
Re-staging	27 (43%)
Therapy response	34 (54%)
Prior medical treatment	
Sandostatin	9
Sandostatin + PRRT	26
Sandostatin + chemo	8
Combined	9
Surgery	3
None	8

GEP, gastro-entero-pancreatic; MRI, magnetic resonance imaging; NET, neuroendocrine tumors; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy.

While 9 of these patients received only Sandostatin treatment, 26 received Lu-177 DOTA TATE treatment also. Apart from these, 8 patients received chemotherapy. In addition, 9 patients received combined treatments (peptide receptor radionuclide therapy (PRRT), chemotherapy, targeted radionuclide therapy). Patient information is shown in Table 2.

In-House Preparation of Ga-68 DOTA TATE

In-house Ga-68 DOTA TATE synthesis was performed in our radiopharmacy laboratory under the guidance of the technique described by Mueller et al.[17,18] following national regulations and guidelines specified by the European Nuclear Medicine Association.

Positron Emission Tomography/Computed Tomography *Imaging*

The patients gave a mean of 182 ± 10 MBq (range 161-198 MBq) Ga-68 DOTA TATE intravenously. Then, WB PET/MR

Table 3. PET/MRI Sequences

Parameter	T1W 3D LAVA (Non-contrast)	Axial WB Diffusion-W (b = 50 and b = 1000)	T2W Coronal WB STIR
TR/TE (ms)	4.6/2	5200/63.3	Auto 6100/42
Inversion time	N/A	250	180
Slice thickness/ gap (mm)	3.6	6	6
Flip angle (°)	12	90	111
FOV (mm)	440-480	440-480	440-480
Matrix	300×224	98×128	288×160

3D, 3-dimensional; DWI, diffusion-weighted imaging; FOV, field of view; LAVA, liver-accelerated volume acquisition; MRI, magnetic resonance imaging; PET, positron emission tomography; STIR, short-tau inversion recovery; T1W, T1 weighted; T2W, T2 weighted; TE, echo time; TR, repetition time; WB, whole body.

images were acquired with an integrated 3 Tesla PET/MRI scanner (GE Signa PET/MRI; GE Healthcare, Waukesha, Wis, USA) from the vertex to the mid-thigh, approximately 45-60 minutes after the injection of the radiopharmaceutical. Simultaneous MRI sequences are obtained in addition to the PET imaging component and include the 3D dual-echo fast spoiled gradient-recalled echo liver-accelerated volume acquisition (LAVA-FLEX) for MRI-based attenuation correction and non-contrast axial T1-weighted (T1W) 3D LAVA-FLEX for anatomical correlation, followed by coronal T2W short-tau inversion recovery (STIR), axial diffusion-weighted images (DWI) with b = 50 s/mm^2 and b = 1000 s/mm^2 values and apparent diffusion coefficient (ADC) mapping sequences from WB as well as axial T2W sequences from the upper abdomen (Table 3 and Figure 1).

Image Interpretation

Two nuclear medicine specialists (SA and SS) with 11 and 16 years of PET expertise evaluated PET images (jointly with T1W sequences for anatomical correlation). Any bone lesion with increased radiopharmaceutical uptake was a positive finding for PET imaging.

Two radiologists (AEE and CS) with 7 and 11 years of MRI experience evaluated MRI sequences. Lesions showing focal hyperintensity in DWI and STIR sequences associated with focal hypointensity in T1W and ADC sequences were considered positive for MRI. The number of PET-positive or MRI-positive lesions and their locations were counted and documented. Patients with more than 10 bone lesions were counted as having 10 lesions.

Table 4. Patients With or Without Bone Metastasis

	With Bone Metastases	Without Bone Metastases
N	24 (38%)	39 (62%)
Sex (female/male)	10/14	15/24
Mean age (years)	59.6	52.3
Tumor grade		
Grade 1	1	15
Grade 2	10	12
Grade 3	0	2
Unknown	13	10
The primary site of disease		
GEP-NET	14 (22%)	32 (51%)
Lung	3 (5%)	4 (6%)
Other	2 (3%)	1 (2%)
Unknown	5 (8%)	2 (3%)
PET/MRI indications		
Staging	1 (2%)	1 (2%)
Re-staging	7 (11%)	20 (32%)
Therapy response	16 (25%)	18 (28%)
Prior medical treatment		
Sandostatin	3	6
Sandostatin + PRRT	9	17
Sandostatin + chemo	6	2
Combined	5	4
Surgery	0	3
None	1	7

GEP, gastro-entero-pancreatic; MRI, magnetic resonance imaging; NET, neuroendocrine tumors; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy.

In a separate patient-based evaluation, the situation where the findings in TATE or MRI were different was defined as discordant. Discordant results were reviewed with radiologists and nuclear medicine physicians during the second reading session.

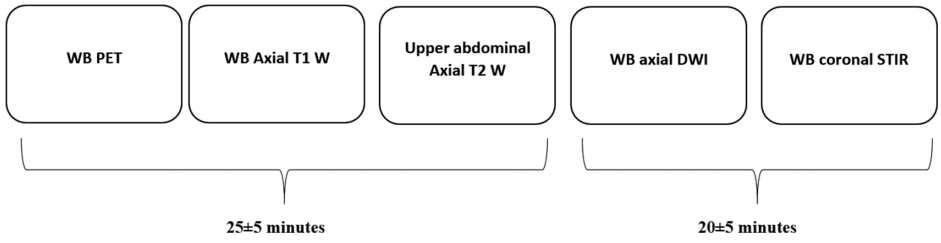

Figure 1. Ga-68 DOTA TATE PET/MRI protocol.

Standard of Reference

Of the 63 patients included in the study, 46 had at least 1 PET/MRI before or after Ga-68 DOTA TATE PET/MRI, and the remaining 17 patients had at least 1 PET/CT scan. Bone biopsy was not performed on any patient. The final decision on the bone lesion was made based on prior/follow-up Ga-68 DOTA TATE PET/MRI or Ga-68 DOTA TATE PET/CT imaging results and clinical status.

Statistical Analysis

Statistical Package for the Social Sciences software version 20 was used for statistical analysis (IBM SPSS Corp., Armonk, NY, USA). The reference standard was used to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of both the modalities. MedCalc's comparison of proportion tool was used to find differences in diagnostic parameters between Ga-68 PET and WB MRI scans (https://www.medcalc.org/calc/comparison_of_proportions.php).

Results

According to the reference standard, we determined bone metastases in 24 (38%) patients and no bone metastases in 39 (62%) patients (Table 4).

Table 5. Diagnostic Parameters of TATE and MRI on Patient-Based Analysis

	TATE (95% CI)	MRI (95% CI)	
	(23 TP, 34 TN, 5 FP, 1 FN)	(17 TP, 34 TN, 5 FP, 7 FN)	*P*
Sensitivity	95.8% (73.9%-99.9%)	70.8% (48.91%-87.38%)	< .001
Specificity	87.2% (72.6%-95.7%)	87.2% (72.57%-95.70%)	1
PPV	82.1% (66.9%-91.3%)	77.3% (59.05%-88.91%)	.504
NPV	97.1% (83.3%-99.6%)	82.9% (72.02%-90.16%)	.008
Accuracy	90.5% (80.4%-96.4%)	80.9% (69.09%-89.75%)	.125

FN, false negative; FP, false positive; MRI, magnetic resonance imaging; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; TATE, Ga-68 DOTA TATE PET; TN, true negative; TP, true positive.

Ga-68 DOTA TATE positron emission tomography imaging was true positive (TP) in 23 patients, true negative (TN) in 34 patients, false positive (FP) in 5 patients, and FN in 1 patient, giving 95.8%

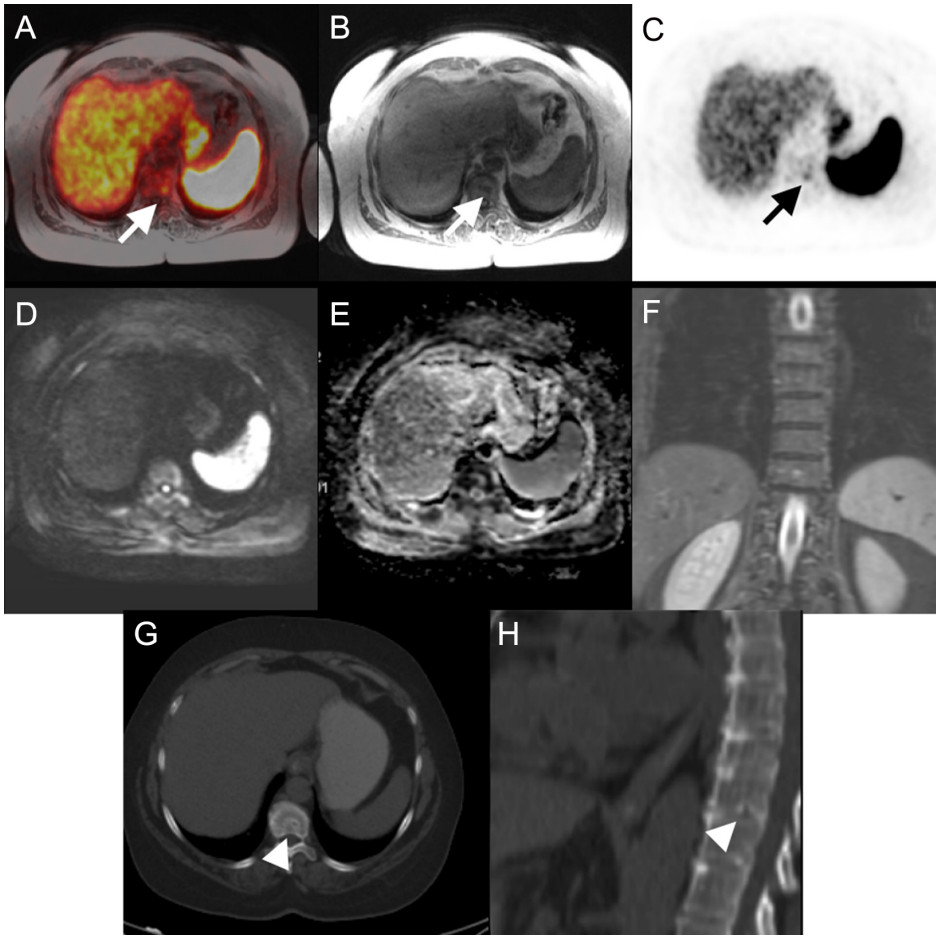

Figure 2. A-H. In the Ga-68 DOTA TATE PET/MRI performed for restaging in a 54-year-old female patient who was followed up with Sandostatin treatment after total gastrectomy for NET of gastric origin, a subcentimetric lesion with focal increased activity uptake was evaluated in favor of metastasis observed in the dorsal 11th vertebral corpus in axial T1W in-phase PET fusion (A), axial T1W in-phase (B), and axial PET images (C) (arrow) and was not detected in axial high *b* value (*b* = 1000) DWI (D), ADC (E), and coronal STIR (F) images. However, due to the findings in the CT sections matching this lesion in the patient's follow-up PET/CT images (G and H), this lesion was considered a Schmorl nodule (arrowhead). ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PET, positron emission tomography; T1W, T1 weighted; STIR, short-tau inversion recovery.

sensitivity, 87.2% specificity, 82.1% PPV, 97.1% NPV, and 90.5% accuracy for demonstrating bone metastases in patient-based evaluation. Magnetic resonance imaging was TP in 17 patients, TN in 34 patients, FP in 5 patients, and FN in 7 patients, resulting in 70.8% sensitivity, 87.2% specificity, 77.3% PPV, 82.9% NPV, and 80.9% accuracy (Table 5).

Seven TATE FP lesions in 5 patients were evaluated according to the standard reference as 6 degenerations (Figure 2) and 1 fracture. Eight lesions in 5 patients were assessed as FP in MRI. Moreover, 4 of them were interpreted as degeneration. Another lesion was hemangioma, positive on MRI but negative on TATE. Apart from these, two MRI-positive lesions that became negative in TATE due to PRRT applied 1 year before imaging and that did not show PET activity and size change in follow-up were evaluated as inactive metastases (TN). Also, according to the standard reference, 1 MR-positive lesion that did not show any significant change in size in the follow-up images was assessed as a benign bone tumor.

According to the standard reference, 9 TP patients had more than 10 lesions. While TATE showed more lesions in 4 of these patients (Figure 3), both the modalities detected a similar number of lesions in the remaining 5 patients. Additionally, PET detected more lesions in 10 of 14 patients with less than 10 metastases (Figure 4). Apart from these, both the modalities noticed an equal number of lesions in 4 patients.

Ga-68 DOTA TATE positron emission tomography and MRI components were concordant in 47 (74.6%) of 63 patients (17 TP, 29 TN, and 1 FN). In the remaining 16 patients, TATE and MRI were discordant, 6 of these patients were TATE TP and MRI FN, and the other 5 were TATE FP and MRI TN. The remaining 5 patients were TATE TN, while MRI was FP.

When PET and MR images were evaluated together, findings suggestive of metastasis on PET were also noticed in MR components in 5 of 16 patients identified as discordant in the separate evaluation. In the remaining 11 patients, inconsistent findings were found in metastasis.

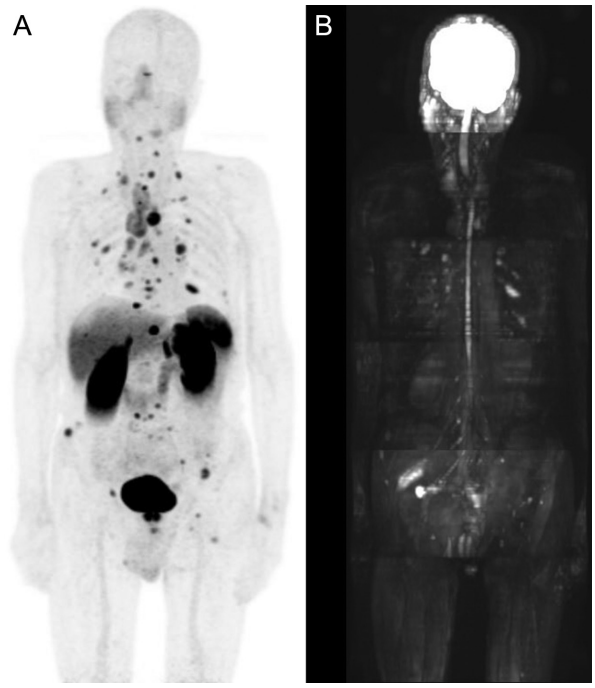

Figure 3. A, B. Ga-68 DOTA TATE PET/MRI performed to evaluate response to treatment in a 71-year-old male patient who was treated with Sandostatin in addition to 10 cycles of PRRT therapy due to metastatic NET of unknown origin showed lymphadenopathies with multiple increased activity uptake consistent with metastasis in mediastinal and cervical lymphatic stations. In addition, PET MIP images (A) show more metastatic lesions in the skeletal system than DWI MIP images (b). DWI, diffusion-weighted imaging; MIP, maximum intensity projection; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy.

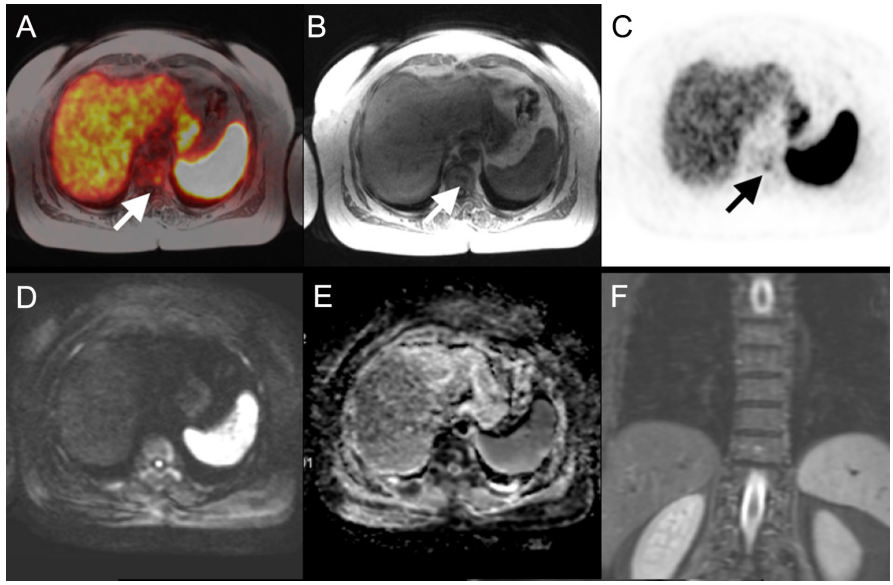

Figure 4. A-F. Ga-68 DOTA TATE PET/MRI performed to evaluate the response to treatment in a 54-year-old female patient who was treated with Sandostatin in addition to 12 cycles of PRRT therapy for metastatic NET of pancreatic origin revealed a primary malignant lesion in the pancreas as well as metastases with multiple increased very intense activity uptake in the liver (not shown). Apart from these, subcentimetric size metastatic lesion with increased activity uptake was observed in the dorsal ninth vertebral corpus in axial T1W phase PET fusion (A), axial T1W in-phase (B), and axial PET images (C) (arrow) and was not observed in high axial b value (b = 1000) DWI (D), ADC (E), and coronal STIR (F) images. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; T1W, T1 weighted; STIR, short-tau inversion recovery.

Clinical Management

Ga-68 DOTA TATE positron emission tomography made the right decision in detecting bone metastases in 57 of 63 patients (90.5%). The clinical approach did not change in 1 patient in which both modalities were FN due to the patient's known distant metastases. In addition, 3 of 5 patients with FP TATE had distant metastases. Ga-68 DOTA TATE positron emission tomography caused overdiagnosis in the remaining 2 (3.2%) patients who did not have distant metastases. When PET and MRI were evaluated, metastasis could not be excluded in TATE-positive lesions.

Discussion

In our study, TATE images showed significantly superior sensitivity and NPV to MRI sequences in detecting bone metastases in NET patients. In addition, although TATE showed superior accuracy, no significant difference was seen. In addition, a similar level of specificity and PPV was observed compared to MRI.

The sensitivity of TATE to detect bone metastases in NET patients agrees with other studies.[14,15,19] On the other hand, TATE shows lower specificity than PET/CT studies.[15,20] The main reason for the lower specificity of TATE can be explained as the absence of a CT component. The T1W sequence used for anatomical correlation cannot replace CT as expected.[21,22] In addition, when PET and MRI are evaluated together, DWI and STIR sequences cannot rule out metastasis in cases where TATE is FP, as in CT.

Our 3T MR images showed higher sensitivity (70% vs. 42%) in detecting bone metastases compared to a 1.5T MRI study in which contrast was not used.[15] On the other hand, it shows a lower sensitivity (70% vs. 96%) than another study with contrast-enhanced imaging protocol.[14]

Whole-body Ga-68 DOTA TATE PET/MRI takes an average of 45 minutes. With contrasted sequences, the acquisition time becomes longer. In our study, DWI and STIR images in the routine protocol do not seem to provide any additional benefit to the clinical approach. The MR sequences are not valuable for evaluating FPs in PET images; they also lead to ambiguous results. In these cases, regional additional PET/CT scans are needed. In light of this information, removing DWI and STIR sequences from the protocol shortens the acquisition time by 20 minutes and may increase patient compliance.

The main limitations of our study are that it included a small patient group and retrospective. In addition, patients have heterogeneous indications. Apart from these, no bone biopsy was performed on any patient for histopathological correlation. In addition, post-contrast sequences could not be obtained due to the length of the current protocol. Another limitation is that we did not investigate the relevance of STIR/DWI sequences in detecting non-osseous metastases.

Conclusion

Positron emission tomography/magnetic resonance imaging using a specific radiopharmaceutical, Ga-68 DOTA TATE, evaluates bone lesions in NET patients with high sensitivity but low specificity. Our study shows that DWI and STIR sequences used in our routine imaging protocol do not contribute to the clinical approach and lead to ambiguous results. It is thought that removing these sequences from the protocol will increase patient compliance, and prospective studies involving large patient groups are needed.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine , (Date: August 18, 2021, Approval No: 178293).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.A., L.U.B.; Design – S.A., A.K.; Supervision – K.S., S.S.; Materials – S.A., A.K., A.E.E., C.S.; Data Collection and/or Processing – A.K.; Analysis and/or Interpretation – S.A., S.S., C.S., A.E.E.; Literature Review – S.A., A.K.; Writing – S.A., A.K., K.S.; Critical Review – S.A., K.S.

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