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Research Article

Gallium-68-DOTATATE PET/CT for phosphaturic mesenchymal tumor localization in suspected tumor-induced osteomalacia

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Abstract

Gallium-68-DOTA-Tyr3-Octreotate (Ga-68-DOTATATE) positron emission tomography/computed tomography (PET/CT) has recently been shown to have utility for the localization of phosphaturic mesenchymal tumors (PMT) that cause tumor-induced osteomalacia (TIO), a rare renal phosphate-wasting disorder. The aim of this study was to evaluate the accuracy of Ga-68-DOTATATE PET/CT in localizing PMTs causing TIO and to compare its performance with other functional imaging modalities. Prospective recruitment and retrospective chart review of 30 patients with suspected TIO and evaluation with Ga-68-DOTATATE PET/CT between 2017 and 2023 were conducted at a tertiary medical center. True positive (TP) lesions were defined by histological confirmation of PMT. There were 22 TP lesions identified among 18 patients, with a mean SUV_{max} of 16.8 (±10.9). Sensitivity, specificity, and accuracy of Ga-68-DOTATATE PET/CT were 85.7%, 77.8%, and 83.3% on patient-based analysis, and 84.6%, 56.3%, and 73.8% on lesion-based analysis. Lesions such as subacute fractures, parathyroid adenomas, thymus uptake, vertebral hemangiomas, bone enchondromas, liver hemangiomas, and avascular necrosis were some of the pitfalls in interpretation. Ga-68-DOTATATE PET/CT led to a significant impact on clinical management in 24 (80%) of patients. The presence of DOTATATE-avid fractures was significantly associated with a localizing scan on univariable (OR 15.0, 95% CI 2.80-110, $p = .001$) and multivariable analysis (OR 9.45, 95% CI 1.33-98.4, $p = .003$). Ga-68-DOTATATE PET/CT has good accuracy for the localization of TIO, with superior sensitivity compared to F-18-FDG PET/CT. This significantly impacted clinical treatment decisions. Although DOTATATE-avid fractures may be a source of false positives, they may also indicate a higher probability of a localizing study.

Keywords: Ga-68-DOTATATE PET, phosphaturic mesenchymal tumor, localization, tumor-induced osteomalacia

Lay Summary

Tumor-induced osteomalacia (TIO) is a rare condition that causes soft bones (osteomalacia) due to abnormal phosphate loss in the urine. Localization of this tumor is key for surgical removal and cure. We studied the utility of Gallium-68-DOTA-Tyr3-Octreotate (Ga-68-DOTATATE) positron emission tomography/computed tomography (PET/CT) in the localization of the tumor in 30 patients suspected to have TIO. The scan had good accuracy when analyzed by both the number of patients and the number of lesions. Its sensitivity was superior compared to F-18-fluorodeoxyglucose (F-18-FDG) PET/CT. Interestingly, fractures with active DOTATATE tracer uptake also had a higher chance of finding the culprit tumor on the same scan; hence, these fractures should prompt closer review of the images. Overall, Ga-68-DOTATATE PET/CT significantly impacted treatment decisions and should be used as a first-line for localization of TIO.

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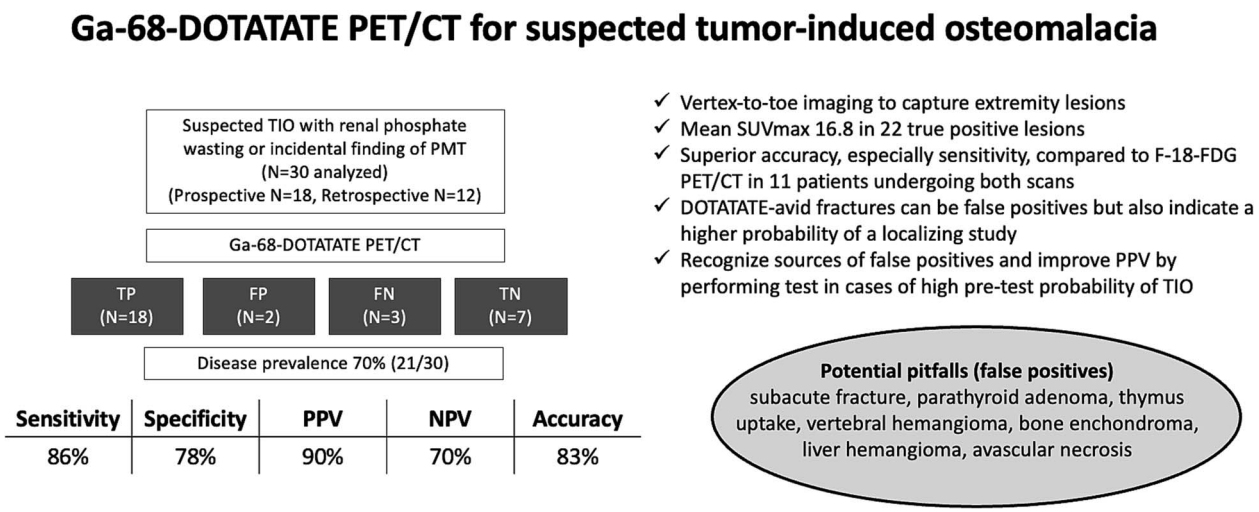
Graphical Abstract



Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic condition that presents as a clinical spectrum that can include hypophosphatemia, fractures, bone pain, and muscular weakness. Osteomalacia is a predominant feature of the disorder and is mediated by excess production of fibroblast growth factor 23 (FGF-23) that causes renal phosphate wasting. In TIO, FGF-23 is secreted by phosphaturic mesenchymal tumors (PMTs), which can occur anatomically anywhere in the body, can arise in bone or soft tissue, and are usually small and slow-growing. Consequently, PMTs are often difficult to localize. However, localization is critical, as surgical resection is curative.

Various imaging modalities, including F-18-fluorodeoxyglucose (F-18-FDG) positron emission tomography/computed tomography (PET/CT), CT, magnetic resonance imaging (MRI), and selective venous sampling for FGF-23, have been used with variable success for tumor localization. Notably, PMTs variably express somatostatin receptors (SSTR 1-5), particularly SSTR2A,[1] which has allowed utilization of SSTR-based functional imaging with octreotide scintigraphy[2] and, more recently, Gallium-68-DOTA-Tyr3-Octreotate (Ga-68-DOTATATE) PET/CT.[3] Ga-68-conjugated somatostatin peptide analogues have become widely available in clinical practice and are primarily utilized for evaluation of neuroendocrine tumors. However, an increasing number of reports demonstrate higher sensitivity with Ga-68-DOTATATE PET/CT than with either F-18-FDG PET/CT or Indium-111 (In-111)-octreotide single photon emission computed tomography (SPECT/CT) for localization of PMTs causing TIO.[4] This has led to the recommendation for Ga-68-DOTATATE PET/CT use as a first-line functional imaging modality by recent expert consensus.[5] However, few studies have reported false positive or true negative findings, and therefore there is limited data regarding the specificity of Ga-68-DOTATATE PET/CT[4,6] in TIO.

The aim of this study was to evaluate the accuracy of Ga-68-DOTATATE PET/CT in localizing PMTs causing TIO to facilitate their identification and to compare the performance of Ga-68-DOTATATE PET/CT with other functional imaging modalities.

Materials and methods

Study design and population

This study consisted of a prospective observational cohort study of adults (aged >18 yr) with suspected TIO evaluated at a single institution who had either (1) persistent hypophosphatemia in the presence of elevated or inappropriately normal FGF23 or (2) incidental finding of a PMT or FGF23-producing tumor with or without hyposphosphatemia. At recruitment, patients with a diagnosis of hypophosphatemic rickets or alternative etiology of hypophosphatemia were excluded. From January 31, 2019 to July 21, 2022, subjects were consecutively recruited to undergo imaging by Ga-68-DOTATATE PET/CT, with written informed consent obtained. With an expected sensitivity and specificity of 90% and an estimated disease prevalence of 50%, a minimum sample size of 18 was required to report specificity and sensitivity with a precision of 20%, based on a target significance level of 95%.[7] The study was approved by the Mayo Clinic Institutional Review Board (IRB #17-008120). This study cohort also encompassed patients who underwent Ga-68-DOTATATE-PET/CT for localization of suspected TIO at our institution between January 1, 2017 and October 1, 2023, which included patients evaluated before the study was opened, and after it met enrollment. These patients were included in the cohort only if they fulfilled the prospective study inclusion and exclusion criteria. All retrospectively analyzed patients were also included in the overall analysis. In order to perform sensitivity and specificity analyses, patients were excluded from the analysis if a diagnosis (TIO or otherwise) was not established at the last follow-up, elaborated on in "Standard of Truth." Patient demographics, biochemistry, imaging, pathology findings, and clinical outcomes were abstracted from the electronic patient medical record.

Biochemistry

In our institution, a C-terminal assay for serum FGF-23 (Immutopics, Quidel Corporation), a 2-site enzyme-linked immunosorbent, was available until March 1, 2021. An intact FGF-23 assay (Medfrontier), a sequential sandwich chemiluminescent enzyme immunoassay, was implemented after February 11, 2020, with a nearly 1-yr overlap period during

which both assays were available. To facilitate a comparison of the differentially measured FGF-23 values in the study, FGF-23 levels were expressed as a function of the fold increase that the measured value exceeded the upper limit of the normal range (×ULN).

Urine collection for calculation of percent tubular reabsorption of phosphate (TRP) was obtained by 24-hr urine sample, paired with same-day fasting blood sample for phosphate and creatinine, calculated as follows:[8]

$$100 \times \left(1 - \frac{\text{urine phosphate} \times \text{serum creatinine}}{\text{serum phosphate} \times \text{urine creatinine}}\right).$$

The tubular maximum reabsorption of phosphate to glomerular filtration ratio (TmP/GFR) was then derived by the following equations.[8]

For TRP < 0.86, TmP/GFR = TRP × phosphorus.

For TRP > 0.86, TmP/GFR = phosphorus × (0.3 × TRP)/[1 − (0.8 − TRP)].

Imaging

Ga-68-DOTATATE PET/CT imaging was performed from the vertex to the toes with imaging initiated 60 min after injection of approximately 5 mCi of Ga-68-DOTATATE. Low dose, non-contrast free-breathing CT images were acquired for attenuation correction and anatomic localization. Maximum standardized uptake values (SUV_{max}) were normalized by body weight. Images were interpreted by consultant radiologists unblinded to available clinical data for clinical-radiological correlation and later confirmed by the same consultant radiologist (S.M.B.) for consistency. Imaging was considered positive if Ga-68-DOTATATE uptake was abnormal and of greater intensity than background or physiologic activity. Imaging was considered negative when only physiologic activity was observed, or when mildly increased activity was reported as attributable to reactive changes or known confounders (eg, recent fractures, osseous hemangiomas, etc.).

Targeted anatomic imaging, including CT or MRI, was performed for indeterminate or suspicious lesion(s), or in symptomatic sites as clinically indicated in accordance with global consensus guidelines.[6] When patients had previously undergone other functional imaging such as FDG-18 PET/CT, In-111-Octreotide scintigraphy with or without SPECT/CT, and/or whole-body Technetium-99m-sestamibi (WB Tc-99m-sestamibi) scintigraphy with or without SPECT/CT for localization, these findings were also reviewed by the consultant radiologist.

Follow-up Ga-68-DOTATATE-PET/CT was not required after lesion-directed treatment of a suspected lesion, as histological confirmation of PMT was deemed as the gold standard for a true positive (TP) lesion, and analyzing response to therapy was beyond the aims of the present study.

Standard of truth

Figure 1 illustrates the approach used to precisely categorize the patient or lesion using clinical and follow-up data. The diagnosis of TIO was clinical, as defined by (1) renal phosphate wasting with no other identified cause, increased or inappropriately normal FGF-23 associated with a paired serum phosphate, low or inappropriately normal $1,25(OH)_2D$, no significant family history of disordered phosphate metabolism, negative genetic testing (if indicated), and no spontaneous recovery,[6] or (2) A PMT or an FGF23-producing tumor identified on histology with or without hypophosphatemia as non-phosphaturic variants of classic PMT are considered early TIO.[9,10] True positives were defined by histological confirmation of PMT of mixed connective tissue variant according to that described by Folpe et al.[11] If a Ga-68-DOTATATE-avid lesion was anatomically correlated with CT or MRI and suspected to be the culprit lesion, the lesion was excluded from analysis if the patient did not undergo surgery or biopsy, as such lesions were considered to be indeterminate in the absence of histological confirmation.

False negatives were defined as those with a clinical diagnosis of TIO with no possible alternative explanation for the clinical presentation and non-localizing Ga-68-DOTATATE PET/CT imaging. If patients with suspected TIO and non-localizing Ga-68-DOTATATE PET/CT imaging were aged <40 yr at presentation and did not undergo genetic testing, they were also considered to be indeterminate and were excluded from analysis.

False positives were defined as those with positive Ga-68-DOTATATE PET/CT as described above, but with either a lack of correlation on anatomical CT or MRI or in patients who underwent suspected lesion biopsy, which by pathologic analysis did not represent a PMT. True negatives were defined as those with negative Ga-68-DOTATATE PET/CT as described above and either a subsequent alternative diagnosis made or spontaneous resolution of hypophosphatemia without the need for phosphate supplementation.

Sensitivity, specificity, accuracy, positive predictive values (PPVs), and negative predictive values (NPVs) were reported for both patient-based and lesion-based analyses.

Statistical analysis

Categorical data were presented as numbers and percentages, and continuous variables as mean (±SD) or median (interquartile range, IQR) according to the normalcy of distribution. Characteristics between patients with localizing imaging and others were compared with one-way ANOVA, Kruskal–Wallis, and Fisher's exact tests as appropriate. The Spearman's rank correlation coefficient (r_s) was used to evaluate the correlation between the maximum standardized uptake value (SUV_{max}) of TP lesions and tumor size. Univariate and multivariate logistic regression models were fit to identify factors associated with localizing imaging. Considering that the number of patients with localizing imaging was small, limited covariates with $p < .1$ on univariate analyses were included to avoid overfitting. All analyses were conducted using BlueSky Statistics Software v.10.3 (Bluesky Statistics LLC).

Results

Overall cohort

Thirty-four patients were referred for Ga-68-DOTATATE PET/CT imaging. Within this cohort, 2 patients had positive localization, but one declined surgery and another declined biopsy; both were therefore excluded from the analysis. Another patient with non-localizing imaging had a clinical diagnosis of TIO with a family history that was negative for osteomalacia, metabolic bone disease, or rickets but was excluded from analyses as he was young (age 36 at

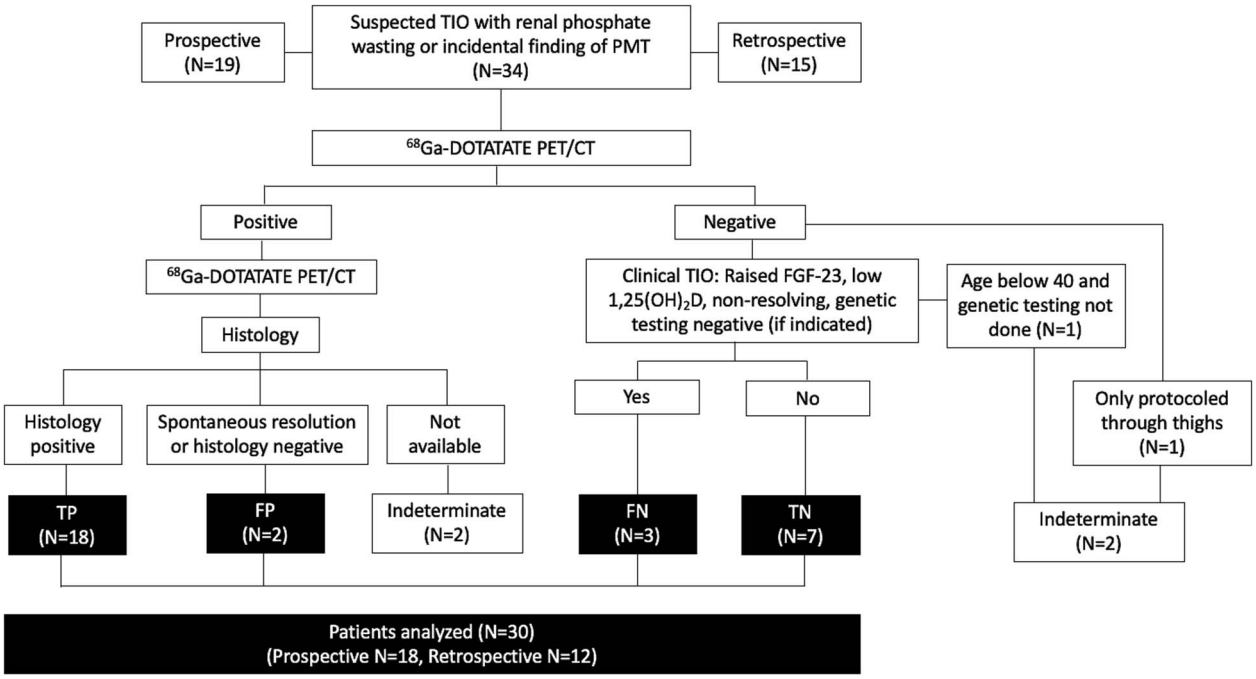


Figure 1. Flowchart of patient classification. Abbreviations: PET, positron emission tomography; CT, computed tomography; FN, false negative; FP, false positive; MRI, magnetic resonance imaging; PMT, phosphaturic mesenchymal tumor; TIO, tumor-induced osteomalacia; TN, true negative; TP, true positive.

presentation) and did not undergo genetic testing. One patient with non-localizing imaging was mistakenly imaged only from the vertex through the thighs, rather than through the toes. Hence, 4 cases were considered indeterminate. Therefore, 30 total patients were included in our study, of which 18 were prospectively recruited and 12 were retrospectively included (Figure 1). 22 had TIO as defined clinically, of which 18 were localizing and 4 were non-localizing.

The mean age of the cohort was 52.6 (±13.4) yr, and 13 (43.3%) were male (Table 1). Median serum phosphate level was 1.6 (IQR 1.4-1.9) mg/dL, and median serum FGF-23 level was elevated 1.68 (IQR 0.83-5.80) times ULN. FGF-23 values were available in all patients, with the majority (66.7%) measured using the C-terminal assay. All patients with available TmP/GFR values had evidence of renal phosphate wasting, as demonstrated by TmP/GFR values below the reference range. The median duration from symptom onset to presentation at our institution was 39.1 (IQR 25.9-55.7) months, and follow-up duration was 34.4 (IQR 12.6-64.0) mo. Five patients (16.7%) underwent genetic testing for a panel of genes associated with hypophosphatemia, of which two revealed pathogenic ENPP1 mutations and three were negative for any known pathogenic mutations.

Patients with positive Ga-68-DOTATATE PET/CT localization

There were 29 Ga-68-DOTATATE-avid lesions identified among 20 patients. Of the 20 patients with positive Ga-68-DOTATATE localization, 18 patients were classified as TPs (Table 2), and two as false positives, giving a PPV of 90.0% (Table 3). Of the 18 patients with TP scans, approximately half of the culprit lesions were localized to bone, with the other half localized to soft tissues (Table 2). Median tumor size was 2.2 (IQR 1.5-4.3) cm. In descending order of frequency, tumors were localized to the head and neck (33.3%), spine (22.2%), lower limbs and trunk (each 16.7%), and upper limbs (11.1%). All patients had a histological diagnosis of PMT. One patient (Subject 27) with a DOTATATE-avid nasal cavity tumor was shown to have a non-phosphaturic PMT. The mean SUV_{max} of TP lesions was 16.8 (±10.9). Tumor size did not correlate with SUV_{max} ($r_s = 0.268$, $p = .299$).

Figure 2 illustrates four localized cases of TIO with variably located tumors from the head to the feet. Cure was achieved in 13 of 18 (72.2%) patients with a localized TP lesion, as defined by achievement of normophosphatemia without the need for supplementation. All 13 cases were cured with surgical resection. In the five patients with persistent disease, one had metastatic disease despite three surgical resections at the site of the primary tumor (Subject 4), two had persistent disease after ablative approaches (cryoablation and radiofrequency ablation) of vertebral body tumors (Subjects 9 and 14), and two patients had persistent disease in the right trapezius muscle and left skull base despite surgical resections (Subjects 3 and 16). Subject 3 (Figure 3), who had persistent disease and multifocal local recurrence despite three surgical excisions over the course of 10 yr, was reported to be a surgically difficult candidate, as the PMT was in close proximity to a neurovascular bundle and required fragmentation at the time of removal. Subject 16, previously described in a case report,[12] was diagnosed with metastatic gastric cancer, which he succumbed to shortly after PMT excision from the left skull base. He experienced multiple other electrolyte abnormalities, including mild hypophosphatemia, during his course of chemotherapy, which was not further evaluated; hence, it is uncertain if TIO cure was achieved.

Out of 18 TP patients, seven patients classified as Ga-68-DOTATATE TPs also had prior alternative functional imaging performed. Two patients underwent WB Tc-99m-sestamibi SPECT/CT, two patients underwent F-18-FDG PET/CT, and three patients underwent both F-18-FDG PET/CT and In-111-Octreotide scintigraphy imaging (Table S1). Subject 15

Table 1. Baseline characteristics and biochemistry.

Baseline characteristics	Total ($n = 30$)	Prospective ($n = 18$)	Retrospective ($n = 12$)	Normal reference range
Age of presentation, yr	52.6 (13.4)	53.0 (13.8)	52.0 (13.3)	
Sex: male, *n* (%)	13 (43.3)	8 (44.4)	5 (41.7)	
Presenting symptoms, *n* (%)				
Fracture	21 (70.0)	12 (66.7)	9 (75.0)	
Pain	18 (60.0)	11 (61.1)	7 (58.3)	
Weakness	13 (43.3)	7 (38.9)	6 (50.0)	
Hypophosphatemia	19 (63.3)	13 (72.2)	6 (50.0)	
Biochemistry				
FGF-23 level at diagnosis				
C-terminal assay, RU/mL	243 (136-521) ($N = 20$)	170 (125-347) ($N = 11$)	336 (236-630) ($N = 9$)	<180
Intact assay, pg/mL	448 (150-983) ($N = 10$)	932 (217-1138) ($N = 7$)	368 (203-448) ($N = 3$)	<59
FGF-23, xULN	1.68 (0.83-5.80)	1.40 (0.83-5.73)	2.28 (1.16-5.52)	
Phosphorus, mg/dL	1.6 (1.4-1.9)	1.7 (1.5-1.9)	1.5 (1.4-1.9)	2.5-4.5
Creatinine, mg/dL	0.88 (0.71-1.00)	0.81 (0.69-0.95)	0.90 (0.84-1.07)	Male 0.74-1.35, Female 0.59-1.04
Calcium, mg/dL	9.2 (8.9-9.6)	9.2 (8.9-9.6)	9.2 (8.9-9.3)	8.9-10.1
Intact PTH, pg/mL	59 (43-85) ($N = 27$)	53 (40-85) ($N = 17$)	60 (52-74) ($N = 10$)	15-65
25(OH)D, ng/mL	43 (18) ($N = 29$)	45.5 (19.5)	40.1 (16.3) ($N = 11$)	Optimal >30
$1,25(OH)_2D$, pg/mL	26.2 (16.4) ($N = 26$)	25.8 (18.5) ($N = 17$)	27.0 (12.5) ($N = 9$)	18-64
ALP, U/L	152 (84-230) ($N = 29$)	160 (84-234) ($N = 17$)	143 (98-202)	Male 40-129, Female 35-104
TRP, %	65.0 (50.5-71.3) ($N = 22$)	69.7 (61.8-74.1) ($N = 13$)	49.1 (41.4-65.6) ($N = 9$)	>80
TmP/GFR, mg/dL	1.07 (0.91-1.36) ($N = 22$)	1.20 (0.95-1.50) ($N = 13$)	0.98 (0.69-1.10) ($N = 9$)	2.6-4.4

Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, total alkaline phosphatase; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; TmP/GFR, tubular maximum reabsorption of phosphate to glomerular filtration rate; TRP, tubular reabsorption of phosphate; xULN, times upper limit of normal. Numbers are indicated for cells with missing values.

Table 2. Tumor characteristics in 18 patients with true positive lesions on ^{68}Ga-DOTATATE PET/CT imaging.

Characteristic	Value	Comments
Malignant, *n* (%)	1 (5.6)	
Tissue: bone, *n* (%)	10 (55.6)	
Location, *n* (%)		
Spine	4 (22.2)	
Trunk	3 (16.7)	
Head and neck	6 (33.3)	
Upper limbs	2 (11.1)	
Lower limbs	3 (16.7)	
Size, cm	2.2 (1.5-4.3)	
SUV_{max}	16.8 (10.9)	
PMT on histology, *n* (%)	18 (100)	
Duration from diagnosis to localization, mo	6.6 (4.2-9.1)	
Functional imaging attempted, *n* (%)		
^{68}Ga-DOTATATE PET/CT	18 (100)	
^{18}FDG PET/CT	5 (27.8)	1/5 successful
^{99m}Tc-Sestamibi	2 (11.1)	1/2 successful
^{111}In-Octreoscan	3 (16.7)	2/3 successful
Eventual cure, *n* (%)	13 (72.2)	

Abbreviations: PMT, phosphaturic mesenchymal tumor; SUV_{max}, maximum standardized uptake value.

underwent all three scans. Ga-68-DOTATATE PET/CT and In-111Octreotide SPECT/CT correctly co-localized to the right temporal lobe in Subject 15, while this anatomic site was a false negative with F-18-FDG PET/CT imaging. WB Tc-99m-sestamibi SPECT/CT was concordant with Ga-68-DOTATATE PET/CT in one of the two patients (50%), but PMT uptake on WB Tc-99m-sestamibi was negligible, and this exam would have been difficult to call as positive without the preceding Ga-68-DOTATATE PET/CT (Subject 3, Figure 3). Out of five patients who underwent F-18-FDG PET/CT, only one (20%) correctly identified the culprit lesion, which demonstrated only mildly increased uptake (Subject 5). Of the three patients who underwent In-111-Octreotide scintigraphy, two patients (66.7%) had correct localization,

Table 3. Diagnostic parameters according to patient-based and lesion-based analyses.

	Scan	Result, *N* (%)				Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
		TP	TN	FP	FN					
(A) Patient-based analysis										
Overall analysis (*N* = 30)	^{68}Ga-DOTATATE PET/CT	18 (60.0)	7 (23.3)	2 (6.7) Prevalence = 70.0%	3 (10.0)	85.7	77.8	90.0	70.0	83.3
Subgroup undergoing both scans (*N* = 11)	^{18}FDG PET/CT	1 (9.1)	2 (18.2)	2 (18.2)	6 (54.5)	14.3	50.0	33.3	25.0	27.3
	^{68}Ga-DOTATATE PET/CT	5 (45.5)	4 (36.4)	1 (9.1) Prevalence = 63.6%	1 (9.1)	83.3	80.0	83.3	80.0	81.8
(B) Lesion-based analysis										
Overall analysis	^{68}Ga-DOTATATE PET/CT (*N* = 42)	22 (51.4)	9 (21.4)	7 (16.7) Prevalence = 61.9%	4 (9.5)	84.6	56.3	75.9	69.2	73.8
Subgroup undergoing both scans	^{18}FDG PET/CT (*N* = 16)	1 (6.3)	5 (31.3)	4 (25.0) Prevalence = 43.8%	6 (37.5)	14.3	55.6	20.0	45.6	37.5
	^{68}Ga-DOTATATE PET/CT (*N* = 18)	7 (38.9)	6 (33.3)	3 (16.7) Prevalence = 50.0%	2 (11.1)	77.8	66.7	70.0	75.0	72.2

Abbreviations: TP, true positive; TN, true negative; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

which was concordant with Ga-68-DOTATATE PET/CT and pathology findings.

Two patients had imaging classified as false positives, one of whom had non-localizing TIO. The patient with non-localizing TIO was a 70-yr-old female with severe renal phosphate wasting, intact FGF23 level, which was elevated 21 times ULN, and suppressed $1,25(OH)_2D$. Initial Ga-68-DOTATATE PET/CT showed 2 possible lesions—a superior mediastinal nodule (SUV_{max} 8.8) and an area of mildly avid uptake in the right zygomatic arch (SUV_{max} 3.7). The 2.5 cm superior mediastinal nodule was biopsied and reported to be a parathyroid adenoma, although serum calcium and serum intact PTH were both normal. When the DOTATATE scan was repeated 1 yr later, both the superior mediastinal and mild right zygomatic arch uptakes had resolved; hence, a biopsy on the zygoma was not performed. Furthermore, the very high dose of burosumab (120 mg every 2 wk) required to maintain serum phosphorus near the lower limit of the normal range was out of proportion to the transient and mild degree of zygomatic arch uptake seen initially. The other patient whose imaging was classified as false positive underwent a fine needle aspirate (FNA) of a suspicious left distal femur lesion, which was only mildly avid (SUV_{max} 1.2) on Ga-68-DOTATATE PET/CT, and was determined to be an enchondroma on pathology. This patient was eventually diagnosed with intravenous ferric carboxymaltose-induced hypophosphatemia.

Patients with negative Ga-68-DOTATATE PET/CT localization

Ten patients with suspected TIO had non-localizing Ga-68-DOTATATE PET/CT imaging, of which seven were true negatives and three were false negatives, giving a NPV of 70.0%. One false negative patient (Subject 11) underwent genetic testing for genes associated with inherited hypophosphatemia due to young age of presentation at 26 yr, with genetic testing negative.

Among the 4 patients with non-localizing TIO (3 false negatives, 1 with a false positive lesion), demographics were similar when compared to those with localizing TIO lesions (TPs)—mean age at presentation was 46.9 (±19.3) yr and included 2 males and 2 females (Table S2). Two patients underwent alternative functional imaging exams, which were also non-localizing (1 patient had a negative F-18-FDG PET/CT, and 1 patient had negative imaging across WB Tc-99m-sestamibi SPECT/CT, F-18-FDG PET/CT, and In-111-Octreotide scintigraphy).

Among the 7 patients with true negative scans, 1 was due to intravenous iron-induced hypophosphatemia as noted above, 2 were attributed to pathogenic ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) mutations, and 4 were attributed to intrinsic renal loss of phosphate due to proximal tubular disorders suspected to be either drug-induced or monoclonal gammopathy-associated (Table S2).

Association of PMT lesions and the presence of DOTATATE-avid fractures

Among patients with DOTATATE-avid fractures on Ga-68-DOTATATE PET/CT, a large proportion (94.4%) had either a diagnosis of clinical TIO or a TP lesion on the same scan (83.3%) (Table 4). This is illustrated in Figure 4 (Subject 19), a patient with a large destructive PMT localized

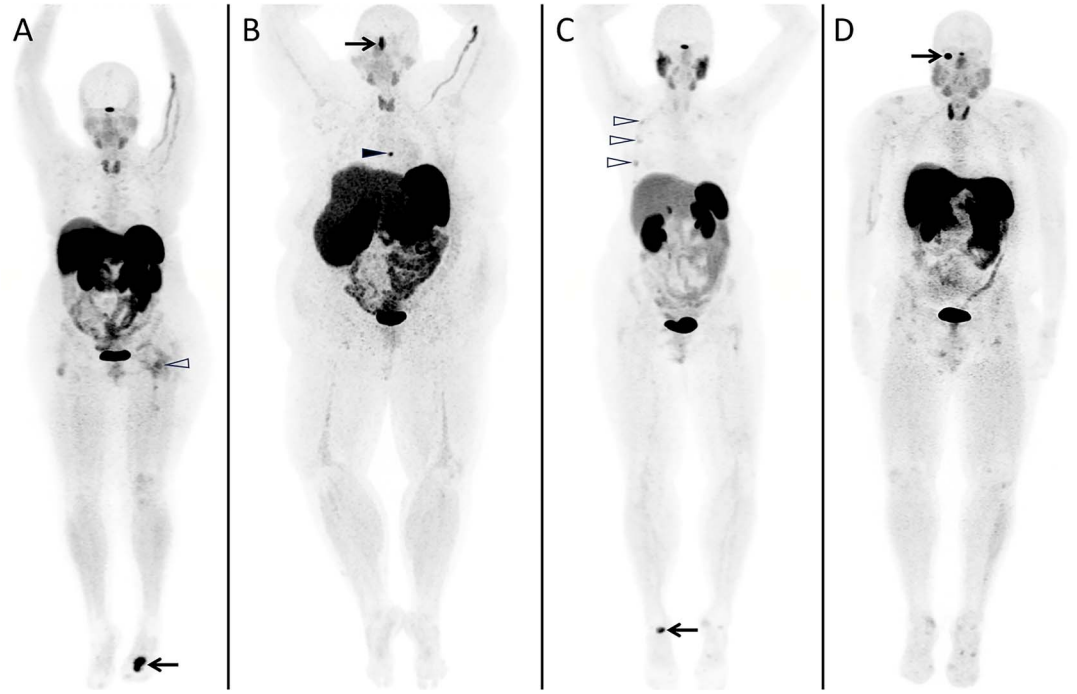


Figure 2. Whole body Ga-68-DOTATATE PET maximum intensity projection images from Subject 17 (A), Subject 27 (B), Subject 8 (C), and Subject 15 (D) demonstrate Ga-68-DOTATATE avid PMTs in the plantar aspect of the left foot (A, arrow), nasal cavity (B, arrow), subcutaneous fat of the right heel (C, arrow), and right middle cranial fossa (D, arrow). These variable lesion locations highlight the need for full body, vertex-to-toes coverage when utilizing Ga-68-DOTATATE PET for PMT localization. Note lower level Ga-68-DOTATATE uptake within insufficiency fractures of the proximal left femur (A, open arrowhead), and multiple right ribs (C, open arrowheads). Subject 27 also demonstrated moderate uptake in a thoracic vertebral hemangioma (B, solid arrowhead), a potential pitfall on Ga-68-DOTATATE PET/CT imaging.

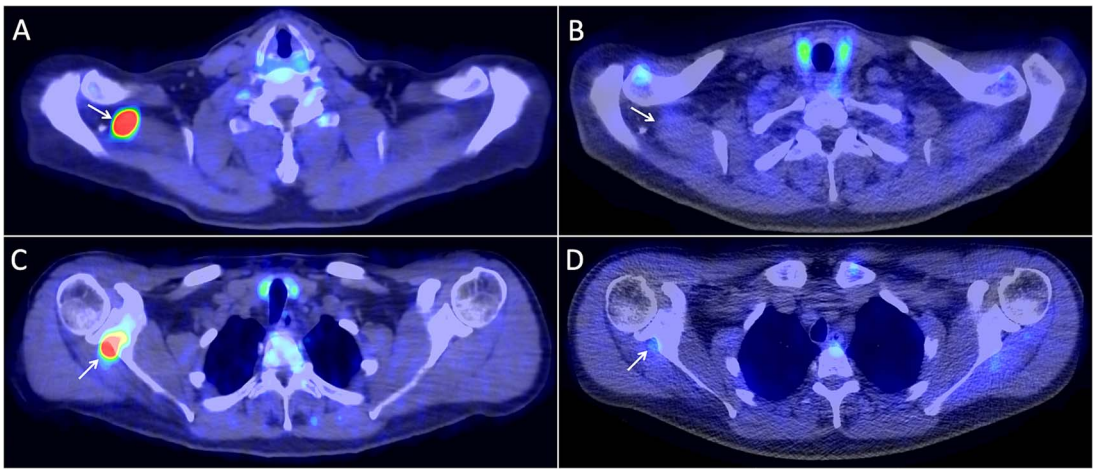


Figure 3. Subject 3 underwent Ga-68-DOTATATE PET/CT (A and C) and WB Tc-99m-sestamibi SPECT/CT (B and D). Axial fused images demonstrate intense Ga-68-DOTATATE uptake in multifocal recurrence about the right shoulder, including within the supraclavicular fossa (arrow, A) and along the spinoglenoid notch (arrow, C). In contrast, there is only faint Tc-99m-sestamibi uptake in these same lesions (arrows, B and D). Imaging examinations were performed one day apart.

to the left acetabulum, with additional focal uptake within a right femoral insufficiency fracture. In contrast, among patients who had no fractures or whose fractures were non-DOTATATE-avid, the proportion having a TP lesion was significantly smaller (25.0%, $p = .002$ compared to those with DOTATATE-avid fractures). Patients with TIO were also more likely to have a fracture than those with an alternative diagnosis (95.2% vs 22.2%, $p < .001$).

Clinical characteristics of patients with localizing imaging and those without were compared (Table S3). In addition to greater fracture prevalence (88.9% vs 41.7%, $p = .013$) and DOTATATE-avid fractures (83.3% vs 25.0%, $p = .002$), patients with localizing imaging (those with a TP lesion) were older (mean age 56.7 vs 46.4 yr, $p = .037$) and had a longer duration from time of symptom onset to first presentation (median 48.2 vs 26.5 mo, $p = .028$). Other biochemistry indices, including baseline serum FGF-23, phosphorus, calcium, creatinine, intact PTH, 25(OH)D, $1,25(OH)_2D$, and ALP levels, were no different between patients with TP PMT lesions and those without.

Table 4. Prevalence of true positive lesions in patients with DOTATATE-avid fractures.

	DOTATATE-avid fractures			Fractures		
	Yes ($N = 18$)	No ($N = 12$)	p-value	Yes ($N = 21$)	No ($N = 9$)	p-value
True positives, *n* (%)	15 (83.3)	3 (25.0)	**.002**	16 (76.2)	2 (22.2)	**.013**
TIO, *n* (%)	17 (94.4)	5 (41.7)	**.003**	20 (95.2)	2 (22.2)	**<.001**

Bold values indicate p-value <0.05.

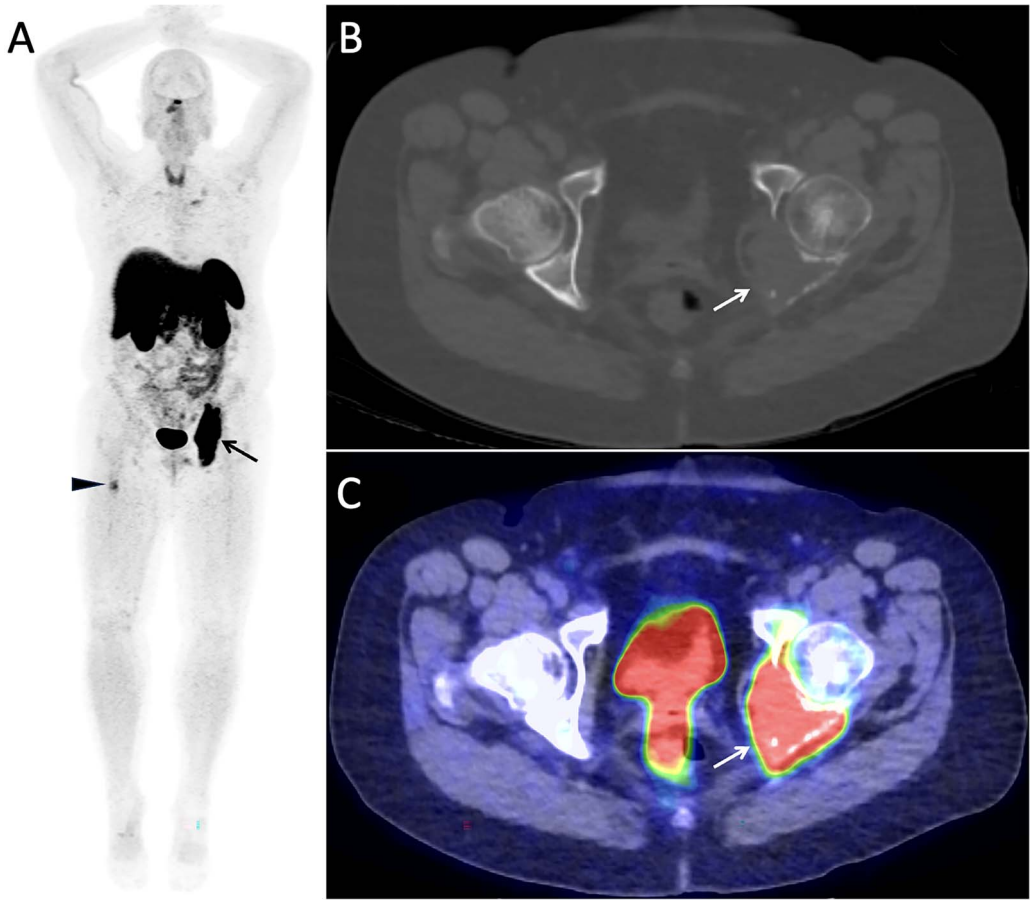


Figure 4. Maximum intensity projection PET (A), axial CT (B), and fused PET/CT (C) images from a Ga-68-DOTATATE PET/CT examination demonstrate intense uptake within a large destructive lytic PMT involving the posterior left acetabulum and left ilium (arrows) (Subject 19). There is also focal uptake within a proximal right femoral insufficiency fracture (A, arrowhead).

In univariable logistic regression, older age (OR 1.07, 95% CI 1.00-1.15, $p = .048$) and the presence of DOTATATE-avid fractures (OR 15.0, 95% CI 2.80-110, $p = .001$) were associated with increased odds of predicting a localizing scan (Table 5). On multivariable analysis, only the presence of DOTATATE-avid fractures was significantly associated with a localizing scan (OR 9.345, 95% CI 1.33-98.4, $p = .002$).

Diagnostic performance of Ga-68-DOTATATE PET/CT and F-18-FDG PET/CT

The diagnostic performance of Ga-68-DOTATATE PET/CT and F-18-FDG PET/CT imaging was evaluated by patient-based and lesion-based analyses. In patient-based analysis in the overall cohort, Ga-68-DOTATATE PET/CT had sensitivity, specificity and accuracy of 85.7%, 77.8%, and 83.3%, respectively (Table 3). On lesion-based analysis, there were 42 suspected lesions evaluated among 30 patients with suspected TIO. The corresponding values for sensitivity, specificity and accuracy were 84.6%, 56.3%, and 73.8%, respectively (Table 3). Sensitivity analysis by subgroup analysis in prospective and retrospective cohorts (Table S4) found similar sensitivity of approximately 80%-90% in both groups, while specificity was lower in the prospective compared to retrospective cohorts for both patient-based and lesion-based analyses.

Seven false positive lesions were identified by Ga-68-DOTATATE PET/CT of 42 lesions evaluated, leading to low specificity, particularly on lesion-based analysis. Utilizing a combination of anatomical imaging, biopsy, or imaging follow-up, these lesions were eventually revealed to represent a subacute fracture, superior mediastinal parathyroid adenoma, transient zygomatic uptake that resolved on subsequent DOTATATE PET/CT, thymus uptake, two separate vertebral hemangiomas, and a tibial enchondroma. Another three lesions were read as suspicious on initial clinical imaging, but were subsequently overread and found to represent a liver hemangioma, right humeral head avascular necrosis, and a subacute rib fracture, and were therefore reclassified

Table 5. Logistic regression of predictors of a localizing scan.

	Univariate (Model 1)			Multivariate (Model 2)[#]		
	p-value	OR	95% CI HR	*p*-value	OR	95% CI OR
Age	**.048**	**1.07**	**1.01-1.15**	.619	1.02	0.94-1.11
Sex: Male	.880	1.12	0.25-5.09	–	–	–
Duration of symptoms	.059	1.03	1.00-1.07	.429	1.01	0.99-1.05
FGF-23, xULN	.345	0.96	0.86-1.05	–	–	–
ALP, U/L	.378	1.00	1.00-1.01	–	–	–
DOTATATE-avid fracture: Yes	**.001**	**15.0**	**2.80-110**	**.001**	**9.45**	**1.33-98.4**

[#] McFadden $R^2 = 0.286$. Abbreviations: ALP, alkaline phosphatase, CI, confidence interval; FGF-23, fibroblast growth factor-23; OR, odds ratio; xULN, times upper limit of normal. Bold values indicate *p*-value <0.05.

as negative. Figure 2 illustrates other lesions demonstrating positive Ga-68-DOTATATE uptake and potential pitfalls in interpretation, such as insufficiency fractures and a vertebral hemangioma.

Eleven patients underwent both Ga-68-DOTATATE PET/CT and F-18-FDG PET/CT imaging, allowing comparison between the 2 modalities. The median interval between both scans was 1 (IQR 0-2.5) yr. In this subgroup analysis, there were 18 suspected lesions in 11 patients with suspected TIO. On both patient-based and lesion-based analyses, Ga-68-DOTATATE PET/CT imaging showed superior sensitivity compared to F-18-FDG PET/CT, leading to greater accuracy. Sensitivity of Ga-68-DOTATATE PET/CT was 83.3% and 77.8% on patient- and lesion-based analyses, as compared to only 14.3% for both types of analyses using F-18-FDG PET/CT (Table 3). Of 6 patients with false negative F-18-FDG PET/CT results, Ga-68-DOTATATE PET/CT was able to correctly identify the culprit lesion in four patients (Subjects 1, 5, 9, and 15), leading to curative surgical resection in 3 patients. Specificity was also higher for Ga-68-DOTATATE PET/CT on both patient- and lesion-based analyses compared to F-18-FDG PET/CT.

Six patients underwent both Ga-68-DOTATATE PET/CT and In-111-Octreotide scintigraphy (three with SPECT/CT), of which 4 had clinical TIO. Median interval between scans was 2.5 (IQR 2-6) yr. One patient had a likely intrinsic renal cause for hypophosphatemia, and another had a pathogenic ENPP1 mutation (Subjects 26 and 29, Table S2). Of the 4 patients with clinical TIO, Ga-68-DOTATATE PET/CT imaging detected the culprit lesion in 3 patients (Subjects 4, 5, and 15, Table S1), while In-111-Octreotide SPECT/CT detected the lesion in 2 patients. In 2 patients with clinical TIO, 2 patient had persistent negative imaging with both Ga-68-DOTATATE PET/CT and In-111-Octreotide scintigraphy (Subject 2), while the other patient (Subject 5) had positive Ga-68-DOTATATE PET/CT localization to the T11 vertebra, which In-111-Octreotide SPECT/CT failed to detect.

Impact on patient management

Sixteen patients (53.3%) had Ga-68-DOTATATE PET/CT performed as the initial functional scan for localization, and 14 (46.7%) had a prior alternative functional scan. Of these 14 patients, Ga-68-DOTATATE PET/CT imaging resulted in a change in management in 12 (85.7%) patients, 7 of whom would have otherwise failed to localize their culprit lesions.

Among these 7 patients, alternative functional imaging in 3 patients pointed towards the culprit lesion, but Ga-68-DOTATATE PET/CT resulted in a more confident diagnosis to guide surgical management. For example, in Subject 3, WB Tc-99m-sestamibi SPECT/CT showed only faint uptake in the right shoulder, as compared to intense Ga-68-DOTATATE uptake (Figure 3). In Subject 5, F-18-FDG PET/CT reported a T11 vertebral lesion as an atypical hemangioma, whereas this was reported to possibly represent a PMT on the Ga-68-DOTATATE PET/CT. In all 3 cases, this led to targeted surgery. Two of three cases achieved surgical cure, while Subject 3 had persistent disease despite correctly targeted surgery, presumably due to lesion fragmentation at the time of surgery.

The 5 patients who had negative Ga-68-DOTATATE PET/CT imaging in addition to other prior functional imaging benefited from a more confident diagnosis of alternative diagnoses (eg, intrinsic renal disorders) and prevented further repeat evaluations in pursuit of a PMT. In Subject 26, negative imaging led to genetic testing, which identified a pathogenic ENPP1 mutation.

Of the 16 patients who had Ga-68-DOTATATE PET/CT performed as the initial functional scan, this resulted in a change in management in 12 (75%) patients. Eleven patients had curative surgery performed without delay as a result, with a cure achieved in 9 patients (81.8%). One patient (Subject 23), aged 47 yr at the time of presentation, was referred for genetic testing after an initial negative Ga-68-DOTATATE PET/CT and found to have a pathogenic ENPP1 mutation, likely accounting for her symptoms.

Hence, in total, 24 of 30 patients (80%) benefitted from Ga-68-DOTATATE PET/CT imaging, as this led to a change in clinical management. However, six patients did not benefit from Ga-68-DOTATATE PET/CT imaging. Four patients who did not benefit had non-localizing TIO. Despite a clinical scenario and laboratory studies consistent with TIO, Ga-68-DOTATATE PET/CT failed to find the culprit tumor. Two patients had ferric carboxymaltose-associated hypophosphatemia, which resolved spontaneously after discontinuation of ferric carboxymaltose, and Ga-68-DOTATATE PET/CT imaging did not change their management.

Ga-68-DOTATATE PET/CT was performed more than once in 5 patients. In addition to detecting the primary tumor site, Ga-68-DOTATATE PET/CT was also successful in detecting local recurrence at surgical sites in 3 patients [Subject 3 (SUV_{max} 21.2), Subject 4 (SUV_{max} 1.3 and 4.8 at the same site in 2 scans done 4 yr apart), and Subject 9 (SUV_{max} 15)], and a pulmonary metastasis (SUV_{max} 4.1), chest wall soft tissue metastasis (SUV_{max} 6.2), and osseous metastasis (SUV_{max} 2.0, 2.5) in Subject 4. This led to re-excision of the local tumor in Subjects 3 and 9 at the site of recurrence. In the patient with localized metastatic disease,

identification of the metastatic lesions led to video-assisted thoracoscopic surgical wedge resection of a lung metastasis and CT-guided radiofrequency ablation of bone metastases in the ribs and vertebral pedicle.

Discussion

This study is one of the largest prospective cohorts of patients evaluated by Ga-68-DOTATATE-PET/CT imaging for PMT localization in TIO. The mean age of 56.7 yr, male:female ratio of approximately 1:1, and equal distribution in bone and soft tissue is consistent with that previously reported.[13,14] The locations of PMTs are diverse and were most common in the head and neck in our cohort, but can localize anywhere from vertex to toes.[15] This highlights the need to perform whole-body imaging from vertex to toes (Figure 2), as standard PET/CT imaging to mid-femur would have missed 3 out of 18 (16.7%) TIO lesions located below the mid-thigh in our study.

Our study reports the sensitivity of Ga-68-DOTATATE PET/CT imaging to be 84%-85% for the localization of TIO. This is in contrast to the 100% sensitivity reported in a retrospective cohort of 42 patients.[16] In that analysis by Zhang et al., of 10 cases with negative Ga-68-DOTATATE PET/CT imaging, all were classified as true negatives even though half of the patients had unexplained hypophosphatemia. Although symptoms were reported to improve with conservative management, symptomatic improvement can also be achieved by normalization of phosphate with calcitriol and phosphate supplementation in non-localizing TIO; hence, it is unclear if the patients in the study of Zhang and colleagues were indeed true negatives in the absence of alternative diagnoses. Other studies reporting zero false negatives have been limited to small retrospective case series.[17–19] Another study, which reported zero false negatives with Ga-68-DOTATATE PET/CT imaging, included 73 patients with adult-onset hypophosphatemic osteomalacia but only included 13 patients with confirmed TIO, with little information on the diagnoses of the 60 patients who were excluded from the analyses.[20]

The accuracy of the performance of Ga-68-DOTATATE PET/CT imaging reported in our study is more comparable to other studies with robust definitions for the standards of truth. El-Maouche et al. reported a prospective study of 11 patients with similar case definitions, which yielded a sensitivity of only 54.5%, likely due to the inclusion of patients with refractory disease who failed multiple localization attempts.[3] A retrospective study of Ga-68-DOTATOC PET/CT imaging in France, which had similar reference standards, reported sensitivity, specificity, and accuracy values of 73%, 67%, and 71%, respectively, in 15 patients.[21]

The specificity of 56%-78% for Ga-68-DOTATATE PET/CT imaging found in our study is relatively low and is even lower for subjects studied prospectively (46%-67%, Table S4). The low specificity is present even when taking into account known areas of physiological uptake in the spleen, adrenals, kidneys, liver, and pituitary gland.[22] False positives were attributed to subacute fractures, vertebral hemangiomas, and a parathyroid adenoma, among others, as cited above. In addition, liver hemangioma and avascular necrosis were lesions nearly misclassified as false positives, stressing the importance of familiarity and expertise in radiologic interpretation, as well as consideration of other diagnoses in clinical context. Of seven false positive lesions, one lesion was clarified to be a false positive on anatomical imaging, one lesion with only mild uptake resolved over time, and three lesions were clarified by negative biopsy results. Only 2 patients with false positive lesions proceeded to undergo surgery. Accordingly, clinicians should be aware of the potential sources of false positive lesions and seek confirmation with anatomic imaging and biopsy before surgical excision. Furthermore, functional imaging should only be requested for patients with a high pretest probability of TIO to reduce the potential for false positives. For example, clinicians should pay attention to a history of intravenous iron infusion, as 2 of 5 patients with DOTATATE-avid lesions on imaging (due to subacute fracture, avascular necrosis, and enchondroma) had resolution of their renal phosphate wasting after change in their intravenous iron formulation. Nonetheless, the specificity of Ga-68-DOTATATE PET/CT imaging adds to the valuable growing evidence of its use in TIO localization, information that has heretofore been rarely reported in existing literature.[6]

DOTATATE-avid subacute fractures have previously been recognized as a common source of false positive lesions,[23] a finding confirmed by our study. Conversely, our study found that in patients with suspected TIO due to renal phosphate wasting, the presence of DOTATATE-avid fractures may be associated with the presence of a TP lesion and should prompt careful scrutiny for a culprit lesion. This may be related to the high prevalence of fractures in patients with TIO (90.9% in our study). In addition, patients in our study with Ga-68-DOTATATE PET/CT localizing imaging (TP lesion) were older and had been symptomatic for a longer duration, findings which may account for more chronic osteomalacia and therefore higher fracture prevalence (and DOTATATE-avid fractures) in this population. However, even after adjustment for potential confounders of age and symptom duration, the presence of DOTATATE-avid fractures remained significantly associated with a higher probability of localizing imaging. Furthermore, chronic hypophosphatemia from non-localizing TIO or other etiologies, such as genetic causes or intrinsic renal tubulopathy is also known to result in chronic osteomalacia and insufficiency fractures.[24] Hence, the marked prevalence of DOTA-avid fractures uniquely in localizing TIO requires further confirmatory studies. This study highlights that not only does the presence of DOTATATE-avid fractures contribute to potential false positives, but such fractures are also associated with a higher likelihood of a localizing study and should prompt careful evaluation.

We also demonstrate superior sensitivity of Ga-68-DOTATATE PET/CT over F-18-FDG PET/CT in 11 patients and over In-111-Octreotide scintigraphy in 6 patients. Two studies have compared Ga-68-DOTATATE PET/CT and F-18-FDG PET/CT head-to-head; notably, both studies agree with our findings even though they included only a handful of patients.[17,25] Agrawal et al. reported positive localization in 5 of 6 patients with Ga-68-DOTATATE PET/CT imaging as compared to only two of four patients with F-18-FDG PET/CT,[17] while Lee et al. reported positive localization in 8 of 12 patients with Ga-68-DOTATATE PET/CT imaging and none of 5 patients undergoing F-18-FDG PET/CT.[25] This reflects that PMTs, which are typically small and slow-growing, have variable and often low uptake of F-18-FDG; as such, F-18-FDG PET/CT imaging is relatively insensitive for PMTs.[26] In comparison, PMTs show high expression

of SSTRs 1-5, and given the high binding affinity of Ga-68-DOTATATE for SSTR2, Ga-68-DOTATATE PET has excellent utility for detecting PMTs.[27] Furthermore, the higher affinity of Ga-68-DOTATATE for SSTRs compared to octreotide, and the improved spatial resolution of PET/CT over SPECT/CT imaging afford many advantages of Ga-68-DOTATATE PET/CT over traditional SSTR imaging.[22] A high mean SUV_{max} of 16.8 (±10.9) of culprit tumors in our study is comparable to that reported elsewhere,[25] and is reflective of the high SSTR affinity of Ga-68-DOTATATE. Importantly, the improved sensitivity of Ga-68-DOTATATE PET/CT allowed for the confident identification of PMTs in nearly half of patients in this study who would not otherwise have had their occult tumors localized and treated, despite other prior functional imaging. Finally, although Ga-68-DOTATATE PET/CT is substantially more costly than F-18-FDG PET/CT imaging, we would argue that the costs of continued morbidity, including progressive disability, pill burden, chronic medical complications of long-term medical therapy (tertiary hyperparathyroidism, renal calculi, chronic kidney disease, etc.) and healthcare utilization costs associated with long-term follow-up and management of persistent non-localizing TIO[28,29] outweigh the additional costs of Ga-68-DOTATATE PET/CT imaging.

Although Ga-68-DOTATATE PET/CT imaging had the highest sensitivity for detection of the culprit PMTs in TIO in our study when compared to other functional imaging modalities, in patients with a moderate-to-high clinical index of suspicion (such as our cohort), its NPV of 70% was insufficient to exclude the diagnosis of TIO. Conversely, if used in patients with a low clinical index of suspicion (eg, normal FGF-23 level, high-normal $1,25(OH)_2D$, or spontaneously resolving hypophosphatemia), the NPV may be higher, thereby effectively pointing the clinician towards alternative diagnoses and/or potentially preventing further futile localization studies. However, this approach is not recommended, as an important consideration in such a cohort with low disease prevalence is its suboptimal specificity, which may result in a significant number of false positives and possible morbidity from subsequent biopsy and/or inappropriate treatments. This implies that functional imaging should be employed for localization of TIO only after a confirmed clinical diagnosis of TIO in patients with a high index of suspicion and is not indicated as an approach for making the diagnosis of TIO in cases in which the clinical and/or biochemical picture is not entirely consistent.

Other indications for the use of Ga-68-DOTATATE PET/CT imaging as illustrated in this study include identification of both local recurrence and metastatic disease. The use of Ga-68-DOTATATE PET/CT for metastatic TIO has rarely been reported.[3] The 1 patient in our study with metastatic TIO had successful localization of multiple metastases, which allowed for targeted treatment of these lesions. Of note, his local recurrence in the shoulder was described to have sarcomatous features on histology, which may explain the relatively low SUV_{max} of 1.3, possibly due to a more poorly-differentiated tumor. There are 2 studies that support the use of Ga-68-DOTATATE PET/CT for recurrent or persistent TIO, although both reported low sensitivity (38.4%-54.5%) for this purpose.[3,13] In contrast, 3/3 patients (100%) in our study with recurrent disease had successful localization with Ga-68-DOTATATE PET/CT imaging, facilitating curative reoperation in these cases. Due to the rarity of recurrent TIO, more data are needed to clarify the effectiveness of Ga-68-DOTATATE PET/CT imaging for identifying recurrent or metastatic TIO lesions.

A strength of our study is the comprehensive evaluation of hypophosphatemic osteomalacia, with 100% of patients having available FGF-23 data, 77% having available TmP/GFR values (with all showing renal phosphate wasting), and 90% having available $1,25(OH)_2D$ values. Few studies have provided sufficient biochemical data, including FGF-23 or $1,25(OH)_2D$ values,[20,25,30] information that is critical for differentiating TIO from other causes of acquired renal phosphate wasting.[6] This contributed to robust definitions for standards of truth for all groups of TP, FP, TN, and FN, unlike previous studies, which reported zero false negatives due to inherent biases.[16–20] Only 2 other small studies had clearly defined standards of truth;[3,21] hence, our study adds substantial and robust data to existing literature. Furthermore, all cases of TPs in our study were verified by histopathological confirmation, and Ga-68-DOTATATE PET/CT imaging was performed from vertex to toes using a protocol that is not necessarily utilized at other centers.[18] These factors lend support to the validity of our findings. Another strength of our study is the inclusion of patients with alternative etiologies of hypophosphatemia, which is reflective of real-world clinical practice where patients may undergo Ga-68-DOTATATE PET/CT as routine evaluation for suspected TIO prior to obtaining negative genetic testing results. A recent meta-analysis reported superior performance of Ga-68-DOTATATE PET/CT imaging for TIO localization, in agreement with our study, although the majority of studies cited in that meta-analysis showed a high risk of bias due to their retrospective nature and interpretation without knowledge of the reference standard.[4] The availability of key biochemical attributes and our use of clear reference standard definitions in our study allow us to conclude that Ga-68-DOTATATE PET/CT imaging is at present the most sensitive modality for TIO localization and also provides reliable information on its specificity.

A limitation of our study is the small number of patients who also underwent alternative functional imaging modalities such as In-111-Octreotide SPECT/CT or WB Tc-99m-sestamibi SPECT/CT imaging due to the rarity of the disease, and these were not performed simultaneously for direct comparison. The small numbers make it difficult to draw definitive conclusions. Second, only a minority of patients in our study underwent genetic testing to exclude genetic causes of hypophosphatemia. Hence, there exists the slight possibility of genetic variants presenting in adulthood that may have spuriously increased the false negative rate and decreased the reported sensitivity. Additionally, novel genetic mutations or variants of unknown significance may exist that even negative genetic testing would not be able to exclude.[31] However, to minimize the risk of erroneous classification, our study excluded patients below the age of 40 who did not undergo genetic testing and who did not have an alternative explanation for their renal phosphate wasting. Third, we cannot exclude potential confirmation bias as full-body CT or MRI was not routinely performed. However, a great majority of patients (29/30) underwent targeted anatomic imaging with CT/MRI in accordance with clinical guidelines, and the only patient who did not undergo confirmatory CT/MRI had curative surgery with resolution of hypophosphatemia and PMT on histology, which is indicative of a correct diagnosis

and localization. Fourth, the confidence interval for the association of DOTATATE-avid fractures and the odds for localizing imaging was broad due to the small number of patients analyzed. Nonetheless, this finding is important and should be further clarified in larger studies. Lastly, our described cohort represents a heterogenous population referred for Ga-68-DOTATATE PET/CT localization, consisting of some patients with confirmed laboratory-based TIO diagnoses and others included during evaluations for renal-phosphate wasting. Notably, some patients had previous failed localization attempts via imaging, whereas for others, Ga-68-DOTATATE PET/CT in our study was a first localization effort. However, such heterogeneity reflects real-world clinical practice, and hence our findings may be applicable to a broad range of scenarios clinicians are likely to encounter in practice given the rarity of TIO.

Conclusion

In the largest prospective study to date of Ga-68-DOTATATE PET/CT imaging for PMT localization of TIO, we confirm the superior sensitivity of Ga-68-DOTATATE PET/CT compared to F-18-FDG PET/CT. As one of the few studies to report the specificity of Ga-68-DOTATATE PET/CT imaging for PMT localization, we highlight important sources of false positive imaging results of which clinicians should be aware, as well as the need for anatomical imaging and/or histopathological confirmation prior to surgical resection. Although DOTATATE-avid fractures may be a source of false positive results, such fractures may also indicate a higher probability of a localizing study and should therefore prompt a close review of the images. An exhaustive consideration of potential etiologies for renal phosphate wasting should be made, including careful clinical and biochemical evaluations for inherited and acquired causes, prior to establishing the clinical diagnosis of TIO. Upon TIO diagnosis, Ga-68-DOTATATE PET/CT imaging should be employed as the first-line functional imaging modality for localization of the culprit tumor. In our study, both in patients with and without prior localization studies, Ga-68-DOTATATE PET/CT imaging significantly impacted clinical treatment decisions.

Author contributions

Caroline W.S. Hoong and Jad G. Sfeir contributed equally to this work.

Caroline W.S. Hoong (Data curation, Formal analysis, Writing—original draft), Jad G. Sfeir (Conceptualization, Project administration, Data curation, Supervision, Writing—review & editing), Matthew T. Drake (Conceptualization, Funding acquisition, Project administration, Writing—review & editing), and Stephen M. Broski (Conceptualization, Funding acquisition, Data curation, Formal analysis, Project administration, Writing—review & editing).

Supplementary material

Supplementary material is available at *JBMR Plus* online.

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Conflicts of interest

None declared. M.T.D. holds the position of Deputy Editor of *JBMR Plus* and has been recused from reviewing or making decisions for the manuscript.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics approval statement

The study was approved by the Mayo Clinic Institutional Review Board (IRB #17-008120).

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