Received:
17 October 2016

Revised:
2 February 2017

Accepted:
6 February 2017

<https://doi.org/10.1259/bjr.20160811>

Cite this article as:

Singh D, Chopra A, Ravina M, Kongara S, Bhatia E, Kumar N, et al. Oncogenic osteomalacia: role of Ga-68 DOTANOC PET/CT scan in identifying the culprit lesion and its management. *Br J Radiol* 2017; **90**: 20160811.

FULL PAPER

Oncogenic osteomalacia: role of Ga-68 DOTANOC PET/CT scan in identifying the culprit lesion and its management

¹DEEPA SINGH, MD, ²ADITI CHOPRA, ¹MUDALSHA RAVINA, MD, ^{2,3}SRIKANT KONGARA, ²EESH BHATIA, ¹NARVESH KUMAR, MD, ²SUSHIL GUPTA, ²SUBHASH YADAV, ²PREETI DABADGHAO, ⁴RAJNIKANT YADAV, ¹VEERESH DUBE, MSc, DMRT, ¹UTHAM KUMAR, MSc, ANMT, ¹MANISH DIXIT, MSc, PhD and ¹SANJAY GAMBHIR, MD

¹Department of Nuclear Medicine, SGPGIMS, Lucknow, India

²Department of Endocrinology, SGPGIMS, Lucknow, India

³Endolife Hospital, Guntur, Andhra Pradesh, India

⁴Department of Radiodiagnosis, SGPGIMS, Lucknow, India

Address correspondence to: Prof. Sanjay Gambhir

E-mail: gaambhir@yahoo.com

Objective: The aim of this study was to evaluate the role of ⁶⁸Ga-DOTANOC positron emission tomography (PET)/CT scan in localization of culprit lesion for biopsy and required intervention [surgical excision/radiofrequency ablation (RFA)] in patients with long-standing oncogenic osteomalacia (OOM)/tumour-induced osteomalacia.

Methods: 17 patients (8 males and 9 females) underwent ⁶⁸Ga-DOTANOC PET/CT scan. The patients referred with clinical and biochemical evidence of hypophosphatemia and raised fibroblast growth factor-23. Qualitative and semi-quantitative parameters were used to identify culprit lesions.

Results: ⁶⁸Ga-DOTANOC PET/CT scan revealed 52 lesions in 17 patients, and 37/52 of these lesions were tracer avid. 26/37 lesions were non-specific focal tracer-avid skeletal lesions (fractures or degenerative changes). 11/37 tracer-avid skeletal lesions present in 9 patients (3 lesions in 1 patient and 1 each in rest of the 8 patients) were highly suspicious for culprit lesions in view of high maximum standardized uptake value (SUV_{max}) (range 1.5–15.4; mean 7.0 ± 4.6), lesion size (0.9–5.0 cm; mean 3.3 ± 1.5) and associated soft-tissue component. During subsequent imaging with CT/MRI, 7/9 patients showed

concordant lesions which were excised or biopsied and histopathologically verified as phosphaturic mesenchymal tumours. Surgical excision was resorted to in most of the detected lesions, and RFA was performed in one patient.

Conclusion: There is some overlap in SUV_{max} between fracture-/bone-associated lesions and culprit lesions with a tendency of most non-culprit lesions to have lower SUV_{max} and no associated soft-tissue component. In such scenario, intensely tracer-avid, larger non-fracture lesions with soft-tissue component may lead to identification of culprit lesion among multiple lesions. Following detection of culprit lesion, surgical removal is the best treatment. RFA is alternative to surgery in cases where surgery is not possible owing to osteopenia/poor bone health.

Advances in knowledge: The main challenge in patients of long-standing OOM is the presence of multiple skeletal lesions (both tumour- or tracer-avid fractures), and it is confusing to identify culprit lesion. This was noted in our study with ⁶⁸Ga-DOTANOC and has not been mentioned in studies performed with ⁶⁸Ga-DOTATATE/TOC PET/CT. In such scenario, ⁶⁸Ga-DOTANOC PET/CT needs to be reviewed and read thoroughly to localize the culprit lesion out of the multiple tracer-avid lesions.

INTRODUCTION

Oncogenic osteomalacia (OOM), also known as tumour-induced osteomalacia (TIO), is a rare syndrome, usually presents with complaints of bone pain, recurrent fractures at multiple sites, decrease in height, muscle atrophy and whole-body weakness.¹ The underlying cause of this acquired paraneoplastic syndrome is a small, usually benign mesenchymal tumour that secretes phosphaturic substances known as phosphatonins. This substance is responsible for the lack of phosphate reabsorption in the proximal tubule of the kidney and thus subsequently leads to humoral

disturbance of phosphate and vitamin D metabolism.² The most studied phosphatonin related to this syndrome is fibroblast growth factor (FGF)-23.^{3,4} The biochemical hallmarks of TIO are hypophosphatemia due to renal phosphate wasting, inappropriately normal or low 1,25-dihydroxy vitamin D and/or elevated plasma FGF-23 level.

Following recognition of syndrome and identification of culprit lesion, the next crucial step is removal of the tumour by surgery or new experimental treatments such as radiofrequency ablation (RFA).⁵ Thus, localization of the

causal tumour or culprit lesion is the most important aspect of early diagnosis and its subsequent management. There are various functional and anatomical imaging modalities available for localizing and characterizing the tumour, e.g. single-photon emission CT (SPECT) or positron emission tomography (PET) octreotide scintigraphy, fluorine-18 (^{18}F) fludeoxyglucose (FDG) PET/CT, CT and MRI. When more than one lesion is detected in the imaging, selective venous sampling with measurement of FGF-23 may be used for further characterization of the lesion.

The characteristic expression of different somatostatin receptors (SSTRs 1–5) in these tumours (most commonly Subtype 2) forms the basis of functional imaging targeting SSTRs.⁶ The PET/CT-based SSTR imaging is advantageous over conventional imaging in terms of improved spatial resolution along with more rapid whole-body functional imaging combined with tomographic anatomic localization. In this, the somatostatin analogues are labelled with gallium (Ga)-68 using the 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) conjugate.

Most of the reported studies have been performed by ^{68}Ga -DOTATATE which has a higher affinity for SSTR-2. However, owing to availability, various other DOTA peptides have also been used. There is dearth of studies comparing ^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC or ^{68}Ga -DOTANOC peptides in this clinical scenario. As quoted in various studies with ^{68}Ga -DOTATATE and ^{68}Ga -DOTATOC, the lesions were pinpointed if identified, but there was no abnormal uptake mentioned at the fracture sites.

The aim of our study was to evaluate the role of ^{68}Ga -DOTANOC PET/CT scan in the localization of culprit lesion in the presence of multiple bony lesions/fractures in various stages of repair and showing variable tracer uptake.

METHODS AND MATERIALS

17 patients with suspected TIO underwent ^{68}Ga -DOTANOC PET/CT in the Department of Nuclear Medicine, in university hospital setting from May 2013 through November 2015. The data were collected retrospectively, and all the patients were followed to see the management following PET/CT scan.

Study design and patient characteristics

We evaluated 17 patients (8 males and 9 females; mean age 42.4 years; age range 18–70 years) with suspected OMM with long symptomatic history referred to us for ^{68}Ga -DOTANOC PET/CT scan.

Written informed consent was obtained prior to the start of study. Plasma FGF-23 (C-terminal) measured by enzyme-linked immunosorbent assay was raised in 15/17 patients at the time of imaging. Plasma FGF-23 value was normal in 2/17 patients and in these patients, PET/CT scan was performed in view of long symptomatic history along with high clinical and biochemical (low serum phosphate) suspicion of TIO. Other biochemical markers were decreased serum phosphorus, low or normal serum calcium, low serum 1,25 dihydroxy vitamin-D and low maximal tubular reabsorption of phosphorus factored for glomerular filtration rate (TmP).

^{68}Ga -DOTANOC positron emission tomography/CT imaging

Gallium-68 was eluted with 0.1-N HCl from “Eckert & Ziegler Germanium-68/Gallium-68” in-house generator and labelled with DOTANOC peptide with fully automatic synthesizer (Modular-Lab; Eckert & Ziegler). Study was acquired 45 $\pm$ 15 min after i.v. injection of approximately 111–148 MBq (3–4 mCi) of ^{68}Ga -DOTANOC in a dedicated Siemens mCT biograph 64-slice PET/CT scanner. First, CT scanning was performed with 64 multidetector CT using care dose four-dimensional technique. Subsequently, PET images were acquired with the acquisition parameter of 3 min per bed position in three-dimensional mode from vertex to toe. Additional spot views of extremities were taken whenever required. Non-attenuation corrected images were also reviewed separately in cases of metallic implants. PET images were reconstructed with iterative reconstruction algorithm using Gaussian filter.

Image interpretation

Images were interpreted qualitatively as well as semi-quantitatively by two experienced nuclear medicine physicians at the Syngo MMWP VE40A workstation which was equipped with fusion software to display PET images (with and without attenuation correction), CT images and fused PET/CT images. Scan findings were correlated with clinical parameters, biochemical markers, conventional imaging work-up and histopathological analysis wherever possible. On PET/CT imaging, tracer-avid lesions were identified. The tracer-avid lesions were suspected of being culprit lesions and also doubtful of being tracer-avid lesions such as fractures in various stages of repair. Non-tracer-avid fractures or lesions were also identified on CT part of PET/CT. In view of multiple lesions in PET/CT scan, lesions with the highest maximum standardized uptake value (SUV_{max}), largest size and with soft-tissue component were suggested for focused anatomic imaging (MRI). Concordant lesions on both PET/CT and anatomical imaging (MRI) were considered to be the culprit lesions.

Statistics

Data were analyzed statistically using SPSS® v. 21 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Values were presented as mean $\pm$ standard deviation, range and numbers.

RESULTS

^{68}Ga -DOTANOC PET/CT scan revealed 52 lesions in 17 patients. 37/52 lesions were tracer avid (fractures/bony degeneration and culprit lesions). Among these, 26/37 lesions were non-specific focal tracer-avid (SUV_{max} range 0.55–4.35; mean 2.6 ± 1.5) skeletal lesions (fractures or degenerative changes). Rest of the 11/37 tracer-avid skeletal lesions present in 9 patients (3 lesions in 1 patient and 1 each in rest 8 patients) were highly suspicious for culprit lesions in view of the high SUV_{max} (SUV_{max} ranged from 1.5 to 15.4; mean 7.0 ± 4.6), lesion size (range 0.9–5.0 cm; mean 3.3 ± 1.5) and were usually associated with soft-tissue components. During subsequent anatomical imaging with CT/MRI, 7 of these 9 patients showed concordant results (Figure 1). These 7 concordant lesions on PET/CT and MRI were later excised or biopsied and histopathologically verified as phosphaturic mesenchymal tumours (PMTs). The rest of the 15/52 lesions were non-tracer-avid skeletal fractures.

Figure 1. MIP (maximum intensity projection) images showing culprit lesions and corresponding fused PET/CT images of 07/09 scan positive patients (arrow): (a) lesion in the proximal shaft of left femur (SUV_{max} 2.2, ~ 5.0 cm cranio-caudally); (b) lesion in the right acetabulum (SUV_{max} 8.0); (c) lesion in the lower end of right humerus (SUV_{max} 6.1); (d) lesion in the posterior wall of left mastoid antrum (SUV_{max} 2.8); (e) culprit lesion in the left hand between 3rd & 4th web space (SUV_{max} 5.7) (arrow) and the subset image showing fracture site at the junction of proximal 2/3rd and distal 1/3rd of right fibula (SUV_{max} 1.4) (arrowhead); (f) lesion in the lateral border of left side of body of mandible (SUV_{max} 5.6, $\sim 2.9 \times 0.59$ cm); (g) culprit lesion involving subcutaneous fat plane in the left gluteal region (SUV_{max} 15.4, $\sim 2.0 \times 1.5$ cm) (arrow) and the subset image showing tracer uptake at the fracture site at mid shaft of left tibia (SUV_{max} 1.6) (arrowhead).

Along with these relatively well-defined lesions in these patients, there were diffuse osteoporotic changes involving the skeleton with non-tracer-avid fractures in 02/17 patients and mixed-avid/non-avid fractures in 3/17 patients. 3/17 patients did not show any abnormal focal tracer uptake or other significant bony abnormality. Patient characteristics are described in [Table 1](#).

DISCUSSION

TIO was first described in 1947, and more than 300 cases have been reported in the literature till now. It can occur in any age group with similar prevalence in males and females. The tumours causing this syndrome are small in size, located within bones or soft tissues and can be seen anywhere from the skull to the toe. In our study, culprit lesions were localized in the mastoid region, mandible, distal humerus, hand, acetabulum, gluteal region and proximal femur.

Histopathologically, TIO was classified as PMTs by Weidner and subdivided into mixed connective tissue (MCT) variant, ossifying fibroma-like variant, non-ossifying fibroma-like variant and osteoblastoma-like variant. The most common variant (approximately 70–80%) reported in the literature is PMT-MCT.⁷ A characteristic finding in these tumours is the consistent ultrastructural features of PMT-MCTs and neuroendocrine

tumours. In our study, all the 7 histopathologically verified lesions were PMT-MCT in nature.

To approach the diagnosis of TIO, serum phosphate should be part of the routine work-up of patients with unexplained muscle weakness, bone pain or fractures, as phosphate is essential for mineralization of bones, signalling between cells, cell membrane function and metabolism. For FGF-23 measurement, the most sensitive and specific assay is intact FGF-23 manufactured by Kainos but used only in research laboratories.⁸

Following the diagnosis of TIO, the main challenge is the localization of culprit lesions, as the lesions are usually very small and commonly located near tendinous insertions. Thus, for the diagnostic work-up, stepwise approach involves functional imaging which covers the entire body from head to toe followed by anatomical imaging to verify the location and further characterize the lesion and selective venous sampling or aspiration in some cases if needed.

The ultimate goal of management following localization is surgical removal of the tumour with a wide margin for complete resection to avoid risk of disease relapse. Another novel possible treatment modality for culprit lesions is RFA for the tumours not amenable to surgery owing to osteopenia,

Table 1. Patient characteristics

Case	Age (years)	Sex	FGF-23 (0–150 RU ml ⁻¹)	S. Phosphorus (3–5 mg dl ⁻¹)	S. Calcium (9–11 mg dl ⁻¹)	S. Alkaline phosphatase (30–150 U/L)	Parathyroid hormone (9–55 pg ml ⁻¹)	S. 25 hydroxy vitamin D (9–47 ng ml ⁻¹)	S. 1,25 dihydroxy vitamin D (16–56 pg ml ⁻¹)	TmPGER (2.5–4.2 mg dl ⁻¹)	TRP (>0.85)	History duration (years)	Suspicious site of primary tumour	HPE proven
1	49	M	550	2.2	8.7	455	17.7	19.77	31.84	1.7	NA	7	Proximal shaft of left femur	Yes
2	52	M	12,000	1.0	10	125	52.3	41.36	NA	0.5	NA	18	Right acetabulum	Yes
3	22	F	229	1.9	8.8	83	54.9	50.02	10.36	0.980	0.151	3	Not detected	–
4	67	M	237	1.8	8.4	193	78	25.12	NA	2.870	1.620	17	Posterior wall of maxillary antrum	Yes
5	70	M	323	2.1	8.5	75	32.3	22.03	4.5	1.260	NA	12	Superior mediastinum (at D ₁ /D ₂ vertebral level)	No
6	32	F	417	3.2	8.43	468	88.2	29.36	NA	1.850	NA	12	Not detected	–
7	31	F	122	2.2	8.72	400	110.10	36	NA	NA	NA	15	Not detected	–
8	18	F	247	1.7	8.3	182	25.7	57.83	70.49	1.9	NA	5	Not detected	–
9	42	F	58.7	4.8	9.8	70	72.7	NA	38.25	1.5	NA	21	Not detected	–
10	38	F	1322.1	1.6	8	541	36.2	31.51	NA	1.804	0.883	4	Not detected	–
11	60	M	2613	1.2	6.8	402	265.2	38.35	23.8	1.120	NA	4	Lower end of right humerus	Yes
12	28	F	495	2.4	8.2	215	154.10	30	NA	NA	NA	5	Not detected	–
13	46	M	237.7	1.4	8.8	178	56.5	54.62	7.45	0.740	NA	3	Right 7th intercostals space	No
14	38	F	272	1.9	8.3	256	129.80	27.34	35.42	0.740	NA	4	Not detected	–
15	43	F	528	1.4	8.3	403	45.9	30.08	7.58	1.660	NA	2	Left hand (b/l 3rd and 4th web space)	Yes
16	45	M	1553	1.0	8.6	271	42.6	31.60	19.7	1.2	NA	1	Left side of body of mandible	Yes
17	27	M	7300	1.2	8.0	245	39.0	75	39.4	0.9	NA	7	Left gluteal region	Yes

F, female; FGF, fibroblast growth factor; GFR, glomerular filtration rate; HPE, Histopathology; M, male; NA, not available; TRP, tubular reabsorption of phosphate.

Table 2. Literature review

Authors and year of publication	Number of patients	Radiopeptide used	Tumour detected	HPE proven
Agrawal et al (2014) ¹⁸	6	Ga-68 DOTATATE	5	5 cases
Jadhav et al (2014) ¹⁹	9	Ga-68 DOTATATE	7 cases	6 cases
Breer et al (2014) ²⁰	5	Ga-68 DOTATATE	5	5
Hesse et al (2007) ²¹	1	Ga-68 DOTANOC	Yes	Yes
von Falck et al (2008) ²²	1	Ga-68 DOTANOC	Yes	Yes
Haeusler et al (2010) ²³	1	Ga-68 DOTATOC	Yes	Yes
Clifton-Bligh et al (2013) ²⁴	6	Ga-68 DOTATATE	In all 6 cases	6 cases
Ho et al (2015) ²⁵	3	Ga-68 DOTATOC	3	3
Zhang et al (2015) ²⁶	54	Ga-68 DOTATATE	44	32
Current study	17	Ga-68 DOTANOC	9	7

location near the joint or poor bone health. Cases where tumours cannot be identified, medical treatment such as properly titrated doses of phosphate solution should be planned to control symptoms and to avoid complications along with periodic surveillance.

For culprit lesion localization, other functional imaging modalities are whole-body ^{99m}Tc-methoxyisobutyl-isonitrile scan and SPECT,⁹ whole-body Tl-201 scintigraphy¹⁰ and octreotide scintigraphy with ^{99m}Tc-Hydrazinonicotinyl-Tyr3-Octreotide,^{11,12} In-111 octreotide¹³ and ¹⁸F-FDG PET/CT.^{14–17}

There are studies in the literature for comparison between conventional nuclear medicine imaging with PET/CT and comparison between ¹⁸F-FDG PET and ⁶⁸Ga-DOTA peptide PET scan.^{18,19} These studies showed that PET scan is better than conventional imaging owing to better spatial resolution and ⁶⁸Ga-DOTA peptide PET scan is better than ¹⁸F-FDG PET scan for tumour localization. In FDG PET, apart from the limitation of lack of receptor-based imaging, the other limitation is lack of poor differentiation due to very slow-growing nature of these tumours and thus, they are less active metabolically and usually skip detection. In a study by Breer et al,²⁰ they reported

Figure 2. A 49-year-old male with complaint of low backache and raised fibroblast growth factor (FGF)-23 (Case 1): ⁶⁸Ga-DOTANOC positron emission tomography (PET)/CT scan localized culprit lesion—(a) maximum intensity projection image revealed a focal area of increased tracer uptake in the left proximal thigh. (b, c) coronal fused PET/CT and CT images revealed an area of increased tracer uptake (maximum standardized uptake value 2.2) with soft-tissue component (measuring 5.0 cm craniocaudally) in the proximal end of left femur. Following localization, tumour was excised with proximal femur endoprosthesis and verified as phosphaturic mesenchymal tumour histopathologically. Images (d) and (e) are coronal and transaxial fused PET/CT images showing very mild tracer uptake at the site of culprit lesion. (f) X-ray image in anteroposterior view showing left proximal lower limb prosthesis *in situ*.

Figure 3. A 52-year-old male with complaint of whole-body pain and raised fibroblast growth factor-23 (Case 2): ^{68}Ga -DOTANOC positron emission tomography (PET)/CT scan localized lesion: (a–f) coronal and transaxial CT, fused PET/CT and PET images and (g) maximum intensity projection (MIP) image revealed focal area of increased tracer uptake [standardized uptake value (SUV_{max}) 8.0] with soft-tissue component at the right acetabulum. Patient was treated with radiofrequency ablation. Subsequently, ^{68}Ga -DOTANOC PET/CT scan for response assessment: (h–m) coronal and transaxial CT, fused PET/CT and PET images and (n) MIP image- revealed near complete resolution of tracer avidity of the lytic lesion at the right acetabulum except mild tracer uptake (SUV_{max} 3.0) at the sclerotic margin.

5 patients of TIO who underwent both ^{111}In octreotide scintigraphy SPECT/CT as well as ^{68}Ga -DOTATATE PET/CT. The result was tumour localization in 1/5 patients by ^{111}In octreotide scintigraphy SPECT/CT and in all 05 patients by ^{68}Ga -DOTATATE PET/CT. Thus, they showed the advantage of octreotide-based PET/CT over SPECT/CT in the tumour localization. A retrospective study performed by Agrawal *et al*¹⁸ to compare the role of ^{18}F -FDG PET/CT and ^{68}Ga -DOTATATE PET/CT in the detection of suspicious primary tumour in six patients of TIO. Tumour was localized in two patients by ^{18}F -FDG and in three patients by ^{68}Ga -DOTATATE tracer. In rest, in two patients, only ^{68}Ga -DOTATATE tracer was used and tumours were localized in both the patients. This study showed the advantage of ^{68}Ga -DOTATATE PET over ^{18}F -FDG PET.

Thus, ^{68}Ga -DOTA peptide PET/CT scan is the best imaging modality as it combines the specificity of octreotide scanning with the sensitivity of PET/CT, having superior spatial resolution and rapid whole-body tomographic imaging in the localization of the culprit lesion in TIO. However, the data available in the literature with the SSTR PET/CT-based imaging in these tumours are limited (Table 2).^{18–26}

Among the variety of somatostatin analogues, most commonly used for imaging are ^{68}Ga -DOTA⁰-Ty³ octreotate (DOTATATE), ^{68}Ga -DOTA⁰-Ty³ octreotide (DOTATOC) and ^{68}Ga -DOTA⁰-Nal³ octreotide (DOTANOC) with variable SSTR subtype specificity. The specific modification of octreotide at Position 3 in ^{68}Ga -DOTANOC leads to higher affinity to SSTR-2 and SSTR-5. As improved affinity is essential for multireceptor tumour targeting, ^{68}Ga -DOTANOC PET tracer seems to be a broad, more sensitive and excellent candidate for targeting suspicious tumour in TIO syndrome.^{27,28}

In the largest series of SSTR-based PET study performed by Zhang *et al*²³ in 54 patients of clinically suspected TIO patients with ^{68}Ga -DOTATATE PET/CT, 44 patients showed positive results. Surgery was performed in 33/44 patients, and post-surgical pathological confirmation was found in 32 patients whose symptoms diminished promptly and the serum phosphate levels became normal. They showed that ^{68}Ga -DOTATATE

PET/CT imaging had a sensitivity of 100% (32/32) and a specificity of 90.9% (10/11) with overall accuracy of 97.7% in the detection of tumours responsible for osteomalacia.²⁶ However, in this large study, the lesions were identified clearly on

Figure 4. A 60-year-old male patient with complaint of gradually progressive pain and unable to walk with raised fibroblast growth factor (FGF)-23 (2613 RU ml^{-1}) (Case 11): ^{68}Ga -DOTANOC positron emission tomography (PET)/CT scan localized culprit lesion: (a–c) coronal fused PET/CT, PET and CT images revealed focal tracer-avid lesion at the distal end of right humerus [maximum standardized uptake values (SUV_{max} 6.1)] along with cortical break and soft-tissue component. (d–f) Sagittal images revealed increased tracer uptake at the head of the right radius (SUV_{max} 2.1). (g–i) Images revealed increased tracer uptake at the base of left index metacarpal bone (SUV_{max} 1.5). (j) A maximum intensity projection image localized the lesion at the distal end of right humerus. Further, MRI scan (k) axial and (l) coronal images showing concordant lesion at the distal end of right humerus. The lesion was excised and (m) and (n) images showing haematoxylin and eosin staining of excised tumour tissue, verified phosphaturic mesenchymal tumour (arrow showing spindle cells).

imaging. In our experience with ^{68}Ga -DOTANOC PET/CT, we were able to find multiple lesions. Uptake was also localized to fractures in various stages of repair. This has not been mentioned in studies performed with DOTATATE/TOC. So, based on size of the lesion and SUV_{max} parameters, lesions were pinpointed for focused anatomic imaging such as MRI which has a better soft-tissue contrast.

There are several previously published studies to suggest the role of two important ^{68}Ga -labelled octreotides (^{68}Ga -DOTANOC or ^{68}Ga -DOTATATE), as PET tracer in the evaluation of TIO. However, there is no head to head comparison of these two peptides in the clinical studies.

In the present study, one of the biopsy-proven patient (Case 1) improved clinically and biochemically following surgical resection

of the culprit lesion (SUV_{max} 2.2, measuring 5.0 cm craniocaudally) localized in the proximal shaft of the left femur (tumour excision with proximal femur endoprosthesis) (Figure 2).

Another biopsy-proven 52-year-old male patient with complaint of whole-body pain since 1996 and raised FGF-23 (Case 2) underwent ^{68}Ga -DOTANOC PET/CT scan, which revealed focal area of increased tracer uptake (SUV_{max} 8.0) with soft-tissue component at the right acetabulum. RFA was performed, which led to partial resolution of the culprit lesion with decrease in SUV_{max} (from 8.0 to 3.0) (Figure 3).

In one patient (Case 11) detected with three suspicious lesions in PET scan, however, the lesion with highest SUV_{max} and soft-tissue component was reported as the causal lesion. The two lesions showed discordant results and one lesion in the lower

end of right humerus (SUV_{max} 6.1) with soft-tissue component showed concordant results on MRI. This concordant lesion was excised and histopathologically verified as PMT (Figure 4). This depicts the importance of associated soft-tissue component with the culprit lesion. Also, as multiple acute or chronic fractures and regenerative changes might show low-grade tracer uptake on PET scan, it is important to identify culprit lesion amongst multiple lesions. As in this case, the lesion with highest SUV_{max} and associated soft-tissue component was the causal lesion.

Another patient (Case 16) detected with suspicious lesion (SUV_{max} 5.6, measuring 2.9×0.59 cm) in close proximity to the lateral border of the left side of the body of the mandible underwent left hemimandibulectomy (mandibular resection and screw fixation with iliac bone graft) and was histopathologically verified as PMT.

One patient (Case 17) with culprit lesion (SUV_{max} 15.4, measuring 2.0×1.5 cm) involving subcutaneous fat plane in the left gluteal region was operated following scan and histopathologically verified as TIO. He had multiple lesions involving the left tibia and bilateral fibulae. However, multiple fractures based on SUV_{max} and fused CT images with no associated soft-tissue component have to be noted.

In rest, 4/9 patients with positive PET scans were followed with MRI/CT scan to further evaluate the suspicious culprit lesions. Among these four patients, two patients (Case 4, culprit lesion involving posterior wall of mastoid antrum, i.e. petrous part of temporal bone on left side with SUV_{max} 2.8; Case 15, culprit lesion involving left hand between third and fourth web space with SUV_{max} 5.7) showed concordant results and later biopsied/operated and verified histopathologically as TIO. Other two patients with discordant results were: a previously operated patient (Case 5) of haemangiopericytoma (transthoracic excision of paraesophageal lesion adjacent to D2 and D3 vertebra) showed lesion in the superior mediastinum at D1/D2 vertebral level in the present scan (SUV_{max} 3.4). However, in view of small size, difficult location and distorted anatomy, it was difficult to operate. Another patient (Case 13) with soft-tissue lesion

involving right seventh intercostal space (SUV_{max} 13.4) is planned for surgery.

Thus, in the field of molecular imaging, ^{68}Ga -DOTA peptide PET/CT is being used to localize the culprit lesion. Most of the previously published studies have been performed with ^{68}Ga -DOTATATE, and none of the ^{68}Ga -DOTANOC/TATE PET study has described the presence of tracer uptake in multiple non-culprit lesions such as degenerative bone disease and/or fractures. The presence of tracer activity at the fractures site in varying stages of healing is likely due to variable spectrum of SSTR expression, as osteoblast in the skeleton tissue also express SSTR2, thus resulting difficulties in detecting the culprit lesion.²⁹

In such scenario, our study reports use of DOTANOC instead of DOTATATE in a series of well-characterized suspected TIO cases to localize the culprit lesion. This is the first study, to the best of the knowledge of the authors, which discusses about multiple benign uptakes in TIO on ^{68}Ga -DOTATNOC imaging. We wish to highlight the fact that identification of the culprit lesion must be carried out tactfully and holistically on imaging along with proper identification of benign uptake and associated fractures must be reported with caution.

CONCLUSION

The main challenge to the clinician in this curable but debilitating TIO syndrome is failure to localize the culprit lesion for definitive management, as most of the lesions in these patients are non-specific tracer-avid or non-avid bony lesions due to fracture in weak osteoporotic bones. Also, there is some overlap in the SUV_{max} between fracture-/bone-associated lesions and the culprit lesion with tendency of most non-culprit lesions to have lower SUV_{max} . In such scenario, intensely tracer-avid larger lesions with associated soft-tissue component may lead to identification of culprit lesion among multiple lesions. Thus, in all clinically suspected cases of hypophosphatemic OMM, multitargeting SSRT-based imaging with ^{68}Ga -DOTANOC PET/CT should be performed as the first-line imaging modality. Following detection of culprit lesion, surgically removal is the best treatment. RFA is alternative to surgery in the cases where surgery is not possible owing to osteopenia/poor bone health/or critical location.

REFERENCES

1. Jan de Beur SM. Tumor-induced osteomalacia. *JAMA* 2005; **294**: 1260–7. doi: <https://doi.org/10.1001/jama.294.10.1260>
2. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol* 2004; **28**: 1–30.
3. Nelson AE, Bligh RC, Mirams M, Gill A, Au A, Clarkson A, et al. Clinical case seminar: fibroblast growth factor 23: a new clinical marker for oncogenic osteomalacia. *J Clin Endocrinol Metab* 2003; **88**: 4088–94. doi: <https://doi.org/10.1210/jc.2002-021919>
4. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A* 2001; **98**: 6500–05. doi: <https://doi.org/10.1073/pnas.101545198>
5. Hesse E, Rosenthal H, Bastian L. Radio-frequency ablation of a tumor causing oncogenic osteomalacia. *N Engl J Med* 2007; **357**: 422–4. doi: <https://doi.org/10.1056/NEJMc070347>
6. Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1–sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. *Eur J Nucl Med* 2001; **28**: 836–46.
7. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. *Cancer* 1987; **59**: 1442–54. doi: [https://doi.org/10.1002/1097-0142\(19870415\)59:8<1442::aid-cncr2820590810>3.0.co;2-q](https://doi.org/10.1002/1097-0142(19870415)59:8<1442::aid-cncr2820590810>3.0.co;2-q)

8. Imel EA, Peacock M, Pitukcheewanont P, Heller HJ, Ward LM, Shulman D, et al. Sensitivity of fibroblast growth factor 23 measurements in tumor-induced osteomalacia. *J Clin Endocrinol Metab* 2006; **91**: 2055–61. doi: <https://doi.org/10.1210/jc.2005-2105>
9. Hodgson SF, Clarke BL, Tebben PJ, Mullan BP, Cooney WP 3rd, Shives TC. Oncogenic osteomalacia: localization of underlying peripheral mesenchymal tumors with use of Tc 99m sestamibi scintigraphy. *Endocr Pract* 2006; **12**: 35–42.
10. Kimizuka T, Ozaki Y, Sumi Y. Usefulness of 201Tl and 99mTc MIBI scintigraphy in a case of oncogenic osteomalacia. *Ann Nucl Med* 2004; **18**: 63–7. doi: <https://doi.org/10.1007/bf02985616>
11. Jing H, Li F, Zhuang H, Wang Z, Tian J, Xing X, et al. Effective detection of the tumors causing osteomalacia using [Tc-99m]-HYNIC-octreotide (99mTc-HYNIC-TOC) whole body scan. *Eur J Radiol* 2013; **82**: 2028–34.
12. Hu FK, Yuan F, Jiang CY, Lv DW, Mao BB, Zhang Q, et al. Tumor-induced osteomalacia with elevated fibroblast growth factor 23: a case of phosphaturic mesenchymal tumor mixed with connective tissue variants and review of the literature. *Chin J Cancer* 2011; **30**: 794–804.
13. Jan de Beur SM, Streeten EA, Civelek AC, McCarthy EF, Uribe L, Marx SJ, et al. Localisation of mesenchymal tumours by somatostatin receptor imaging. *Lancet* 2002; **359**: 761–3.
14. Jagtap VS, Sarathi V, Lila AR, Malhotra G, Sankhe SS, Bandgar T, et al. Tumor-induced osteomalacia: a single center experience. *Endocr Pract* 2011; **17**: 177–84.
15. Dupond JL, Mahammedi H, Prie D, Collin F, Gil H, Blagosklonov O, et al. Oncogenic osteomalacia: diagnostic importance of fibroblast growth factor 23 and F-18 fluorodeoxyglucose PET/CT scan for the diagnosis and follow-up in one case. *Bone* 2005; **36**: 375–8.
16. Roarke MC, Nguyen BD. PET/CT localization of phosphaturic mesenchymal neoplasm causing tumor-induced osteomalacia. *Clin Nucl Med* 2007; **32**: 300–1. doi: <https://doi.org/10.1097/01.rlu.0000257180.03964.51>
17. Khadgawat R, Singh Y, Kansara S, Tandon N, Bal C, Seith A, et al. PET/CT localization of a scapular haemangiopericytoma with tumour-induced osteomalacia. *Singapore Med J* 2009; **50**: 55–7.
18. Agrawal K, Bhadada S, Mittal BR, Shukla J, Sood A, Bhattacharya A, et al. Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia. *Clin Nucl Med* 2015; **40**: 6–10. doi: <https://doi.org/10.1097/RLU.0000000000000460>
19. Jadhav S, Kasaliwal R, Lele V, Rangarajan V, Chandra P, Shah H, et al. Functional imaging in primary tumour-induced osteomalacia: relative performance of FDG PET/CT vs somatostatin receptor-based functional scans: a series of nine patients. *Clin Endocrinol* 2014; **81**: 31–7.
20. Breer S, Brunkhorst T, Beil FT, Peldschus K, Heiland M, Klutmann S, et al. 68Ga DOTATATE PET/CT allows tumor localization in patients with tumor-induced osteomalacia but negative 111In-octreotide SPECT/CT. *Bone* 2014; **64**: 222–7. doi: <https://doi.org/10.1016/j.bone.2014.04.016>
21. Hesse E, Moessinger E, Rosenthal H, Laenger F, Brabant G, Petrich T, et al. Oncogenic osteomalacia: exact tumor localization by co-registration of positron emission and computed tomography. *J Bone Miner Res* 2007; **22**: 158–62.
22. Von Falck C, Rodt T, Rosenthal H, Langer F, Goesling T, Knapp WH, et al. (68)Ga-DOTANOC PET/CT for the detection of a mesenchymal tumor causing oncogenic osteomalacia. *Eur J Nucl Med Mol Imaging* 2008; **35**: 1034.
23. Haeusler G, Freilinger M, Dominkus M, Egerbacher M, Amann G, Kolb A, et al. Tumor-induced hypophosphatemic rickets in an adolescent boy—clinical presentation, diagnosis, and histological findings in growth plate and muscle tissue. *J Clin Endocrinol Metab* 2010; **95**: 4511–7.
24. Clifton-Bligh RJ, Hofman MS, Duncan E, Sim Ie W, Darnell D, Clarkson A, et al. Improving diagnosis of tumor-induced osteomalacia with Gallium-68 DOTATATE PET/CT. *J Clin Endocrinol Metab* 2013; **98**: 687–94.
25. Ho CL. Ga68-DOTA Peptide PET/CT to Detect Occult Mesenchymal Tumor-Inducing Osteomalacia: A Case Series of Three Patients. *Nucl Med Mol Imaging* 2015; **49**: 231–6.
26. Zhang J, Zhu Z, Zhong D, Dang Y, Xing H, Du Y, et al. 68Ga DOTATATE PET/CT is an accurate imaging modality in the detection of culprit tumors causing osteomalacia. *Clin Nucl Med* 2015; **40**: 642–6.
27. Wild D, Schmitt JS, Ginj M, Macke HR, Bernard BF, Krenning E, et al. DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. *Eur J Nucl Med Mol Imaging* 2003; **30**: 1338–47. doi: <https://doi.org/10.1007/s00259-003-1255-5>
28. Wild D, Macke HR, Waser B, Reubi JC, Ginj M, Rasch H, et al. 68Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5. *Eur J Nucl Med Mol Imaging* 2005; **32**: 724. doi: <https://doi.org/10.1007/s00259-004-1697-4>
29. Mackie EJ, Trechsel U, Bruns C. Somatostatin receptors are restricted to a subpopulation of osteoblast-like cells during endochondral bone formation. *Development* 1990; **110**: 1233–9.