

# Utility of Multimodality Approach Including Systemic FGF23 Venous Sampling in Localizing Phosphaturic Mesenchymal Tumors

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## Abstract

**Context:** Tumor-induced osteomalacia (TIO) is one of the most common forms of acquired fibroblast growth factor 23 (FGF23)-related hypophosphatemia and is usually caused by phosphaturic mesenchymal tumors (PMTs). Although the complete resection of PMTs can cure TIO, preoperative localization of tumors by standard imaging modalities is often challenging. In addition to <sup>18</sup>F-fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography (FDG-PET) and <sup>111</sup>In-pentetreotide scintigraphy (SRS), systemic FGF23 venous sampling (FGF23VS) has been used to help localize PMTs in specialized institutions.

**Objective:** This study aimed to evaluate the diagnostic performance of each imaging test and their combinations in localizing PMTs.

**Methods:** In an observational retrospective study of patients with adult-onset FGF23-related osteomalacia who underwent all 3 imaging studies (FDG-PET, SRS, and FGF23VS), the rate of successful preoperative localization of the tumors was evaluated only in the patients with pathological diagnoses of PMTs, considering the possibility that pathogenesis of patients without identified tumors might be due to other causes such as late-onset hereditary FGF23-related hypophosphatemia.

**Results:** A total of 30 Japanese patients with TIO (median age, 60 years [range, 28–87 years]; 10 women [33.3%]) were included in the study. The success rate of preoperative localization for each test and combinations of 2 or 3 tests among 18 patients with PMTs was as follows: 72% (FDG-PET), 72% (SRS), 94% (FGF23VS), 89% (FDG-PET, SRS), 100% (FDG-PET, FGF23VS), 94% (SRS, FGF23VS), and 100% (FDG-PET, SRS, and FGF23VS).

**Conclusion:** We observed the highest localization rate of PMTs in patients with identified PMTs with the combination of FDG-PET and FGF23VS.

**Key Words:** tumor-induced osteomalacia, fibroblast growth factor 23, phosphaturic mesenchymal tumor, <sup>18</sup>F-FDG PET/CT, <sup>111</sup>In-pentetreotide scintigraphy, venous sampling

**Abbreviations:** 1,25(OH)<sub>2</sub>D, 1,25-dihydroxyvitamin D; CT, computed tomography; FGF23, fibroblast growth factor 23; FGF23VS, FGF23 venous sampling; FDG-PET, <sup>18</sup>F-fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; PMT, phosphaturic mesenchymal tumor; SPECT, single photon emission computed tomography; SR-PET/CT, somatostatin receptor PET/CT; SRS, somatostatin receptor scintigraphy; TIO, tumor-induced osteomalacia; Tmp/GFR, tubular maximum transport of phosphate.

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome caused by fibroblast growth factor 23 (FGF23)-

producing phosphaturic mesenchymal tumors (PMTs), usually occurring in bones and soft tissue. The estimated prevalence of

TIO is 0.7 to 5 per 100 000 persons [1-3]. Nevertheless, the actual prevalence is unclear due to the high prevalence of misdiagnosed/undiagnosed cases [4]. Typical clinical symptoms and signs of TIO are nonspecific musculoskeletal symptoms, including progressive muscle and bone pain, weakness, fatigue, and recurrent fractures [5]. Thus, patients with TIO are often initially diagnosed with other skeletal diseases, such as herniated disc, ankylosing spondylitis, spondyloarthritis, and osteoporosis [6].

The detection of hypophosphatemia with relatively high FGF23 levels in adult patients with such musculoskeletal symptoms can help diagnose TIO, except for FGF23-related osteomalacia following the intravenous injection of an iron preparation and alcohol consumption [7-12]. Even after the biochemical diagnosis of TIO, the localization of responsible tumors is often difficult because the responsible tumors are sometimes small and can develop anywhere in the body [2]. Supportive treatment with an oral phosphate preparation and active vitamin D is usually used in patients when tumors are not identified or are surgically unresectable, incompletely resected, or recurring. However, the effect of these palliative measures is limited and is sometimes associated with an increased risk of impaired kidney function [13, 14]. In recent years, the beneficial effects of the anti-FGF23 monoclonal antibody, burosumab, in patients with TIO have been reported [15, 16]. Burosumab has been shown to bind to FGF23 and interfere with its conjugation to the FGFR/Klotho receptor complex, increasing serum phosphate levels and enhancing the healing of fractures [15, 16]. However, a complete, extended resection of PMTs remains the gold standard for TIO and will improve patients' quality of life and reduce the economic burden.

For the successful localization of FGF23-producing PMTs, special imaging techniques other than conventional computed tomography (CT) and magnetic resonance imaging (MRI) have been utilized in TIO [4]. In 2004, our group reported the utility of systemic FGF23 venous sampling (FGF23VS) in localizing PMTs [17], with which we successfully identified 7 PMTs out of 10 TIO patients [18]. In this method, blood samples are typically collected from 10 to 30 sites across the body using a catheter inserted into a femoral vein. Tumors are theoretically located near the site where the FGF23 concentration is highest [17, 18]. While FGF23VS involves invasive procedures, it can provide both anatomical and hormonal information on PMTs, unlike other imaging modalities.

Somatostatin receptor scintigraphy (SRS), such as <sup>111</sup>In-pentetreotide scintigraphy, and somatostatin receptor PET/CT (SR-PET/CT), such as <sup>68</sup>Ga-DOTATOC-PET/CT, <sup>68</sup>Ga-DOTANOC-PET/CT, and <sup>68</sup>Ga-DOTATATE-PET/CT, have been used to localize PMTs in patients with TIO [19-25]. The spatial resolution of SRS is much lower than that of PET/CT (lower sensitivity), and SRS often shows uptake in lesions with inflammation, such as pseudofractures (lower specificity) [25]. While SR-PET/CT provides higher spatial resolution than SRS and accessibility to the test is gradually expanding in several nations, its use is still highly limited in many countries, including Japan [26]. Neither SRS nor SR-PET/CT can differentiate PMTs from other neuroendocrine tumors, which often express somatostatin receptors [26] and 18F-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (FDG-PET) has also been used to localize PMTs [27].

A previous case series of patients with TIO demonstrated the different sensitivities and specificities of various diagnostic modalities [24, 28-30]. To date, however, there is no established diagnostic paradigm of TIO that recommends the ideal sequence or combination of localization studies. In this study, we retrospectively evaluated the diagnostic performance of 3 imaging studies (FDG-PET, SRS, FGF23VS) and their combinations in localizing PMTs in 30 consecutive patients with late-onset FGF23-related osteomalacia.

## Materials and Methods

### Patients

In other facilities where SR-PET/CT is inaccessible, as is the case in Japan, it is common to conduct FDG-PET CT and SRS in a stepwise fashion. Subsequently, in patients with no tumor or multiple culprit tumors, FGF23VS will be recommended as an optional procedure. In contrast, in our facility, the University of Tokyo Hospital, all 3 procedures (FDG-PET, SRS, and FGF23VS) are performed in the clinical trial (UMIN000031742) of patients with late-onset FGF23-related osteomalacia before surgery based on the following concepts. FDG-PET and SRS are targeting different characteristics of the tumors; proliferation capacity and endocrine activity, therefore, the combination of these 2 imaging tests might increase the detection rate of the PMT, and each test provides the information about the different aspects of the tumors. FGF23VS provides us with additional clues for detecting PMTs in patients with negative nuclear scanning and is useful to directly confirm FGF23-producing capacity of the culprit tumors in patients with positive nuclear scanning. In the present clinical trial (UMIN000031742), the cost for FGF23VS was covered by research support from Kyowa Kirin Co. Ltd., while FDG-PET and SRS were covered under the system of national health insurance.

Thirty consecutive patients with late-onset FGF23-related osteomalacia with a history of fractures or pseudofractures who had undergone FDG-PET, SRS, and FGF23VS from March 2014 to December 2020 were included in this study. Patients were excluded from the study if they had a familial history of rickets/osteomalacia or were administered intravenous iron preparation. Of all 30 patients with TIO included in the present study, 19 patients (Cases 1-19) were included in the previous study by Hidaka et al [31]. However, the aim of the current study was pursuit of sensitivity and specificity for each modality with the complete datasets from 30 patients with TIO, which was different from the previous study, in which the main purpose was to clarify the clinical course and outcome of 88 patients with TIO, including participants without each modality performed [31]. All procedures were performed following the ethical standards of the Declaration of Helsinki and were approved by the institutional ethical board of the University of Tokyo Hospital (Ref. P2017016 and G10115). All patients provided written informed consent.

### Evaluation of Biochemical and Clinical Data

The serum phosphate, albumin-adjusted calcium, creatinine, alkaline phosphatase (ALP), bone alkaline phosphate (BAP), intact parathyroid hormone (PTH), FGF23, and 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] data were retrospectively collected from electronic health records in the hospital. Biochemical tests, including serum phosphate,

calcium, albumin, and creatinine, were performed by a LABOSPECT008 (Hitachi, Tokyo, Japan). Intact parathyroid hormone was analyzed using an electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Tokyo, Japan). 1,25(OH)<sub>2</sub>D was measured by radioimmunoassay (RIA) (Fujirebio, Tokyo, Japan). FGF23 values were measured by an FGF-23 ELISA Kit (KAINOS Laboratories, Inc., Tokyo, Japan, RRID: AB\_2782966), which exclusively detects biologically active intact FGF23. The interassay SD and coefficient of variation were 0.74 and 3.8, respectively, while the intraassay SD and coefficient of variation were 0.82 and 2.8, respectively. Tubular maximum transport of phosphate (TmP/GFR) was calculated from values in serum and spot urine according to the nomogram [32]. Clinical data, including age, sex, duration of the disease, use of walking aids, prior surgical history, pathological findings of the tumors, and surgical outcomes, were also collected from electronic health records. In this study, based on a previous report [33], resection of the tumor was regarded as “complete resection” when serum phosphate levels were maintained within the normal range for 2 years after the surgery.

### **<sup>18</sup>F-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography–Computed Tomography**

FDG-PET for the whole body was performed per the latest standard PET imaging protocols. Images were filmed 2 hours after the average injection of 200 MBq of <sup>18</sup>F-fluorodeoxyglucose.

### **<sup>111</sup>In-Pentetreotide Somatostatin Receptor Scintigraphy**

Whole-body SRS was performed by a gamma camera system (E. CAM Signature; Siemens, Toshiba/Siemens, Tokyo, Japan) 4, 24, and 48 hours after the average injection of 200 MBq of <sup>111</sup>In-pentetreotide. A designated radiologist reviewed and located the tumors in the FDG-PET and SRS images before and after FGF23VS.

### **Systemic FGF23 Venous Sampling**

An experienced designated radiologist performed FGF23VS using a catheter inserted into the right femoral vein. Blood samples were taken from 22 sites, including bilateral internal jugular veins, bilateral brachial veins, bilateral subclavian veins, bilateral brachiocephalic veins, the distal superior vena cava, the proximal superior vena cava, the proximal inferior vena cava, the distal inferior vena cava, bilateral common iliac veins, bilateral internal iliac veins, bilateral external iliac veins, bilateral proximal femoral veins, and bilateral distal femoral veins, and then intact FGF23 levels were measured in our laboratory. FGF23VS was usually performed after other imaging studies, and when tumors had been detected before FGF23VS, serum samples were obtained from an additional 1 to 6 sites near the tumors. The complications of FGF23VS were collected from the clinical records within 3 days after FGF23VS. Complications, including nausea (n = 1), pain at the puncture site (n = 1), pain in the shoulders and knees (n = 1), and vasovagal reflex (n = 1), were observed, while none of the patients experienced major adverse events, such as vascular complications.

### **Localization, Resection, and Immunohistochemical Evaluation of PMTs**

Based on the results of FDG-PET, SRS, and FGF23VS, an experienced endocrinologist determined the location of PMTs using additional CT or MRI, where applicable. From April 2013 to March 2016, selected patients without identified tumors after FDG-PET, SRS, and FGF23VS were referred to Kyoto University Hospital to undergo <sup>68</sup>Ga-DOTATOC-PET/CT scans. When tumors were identified, endocrinologists and surgeons discussed whether the patient should undergo surgery based on the location of tumors, the patient’s general health status, and the informed consent from the patient. Immunohistochemical staining was performed at the pathology department using the Ventana BenchMark automated immunostainer (Ventana BenchMark; Ventana Medical Systems Inc., Tucson, AZ) according to the manufacturer’s instructions. We used an anti-human FGF23 monoclonal antibody (FC1, gift courtesy from Kyowa Kirin, Tokyo, Japan, RRID: AB\_2924835) as the primary antibody in this study [34]. Tumors positive for FGF23 by immunohistochemistry were diagnosed as PMTs.

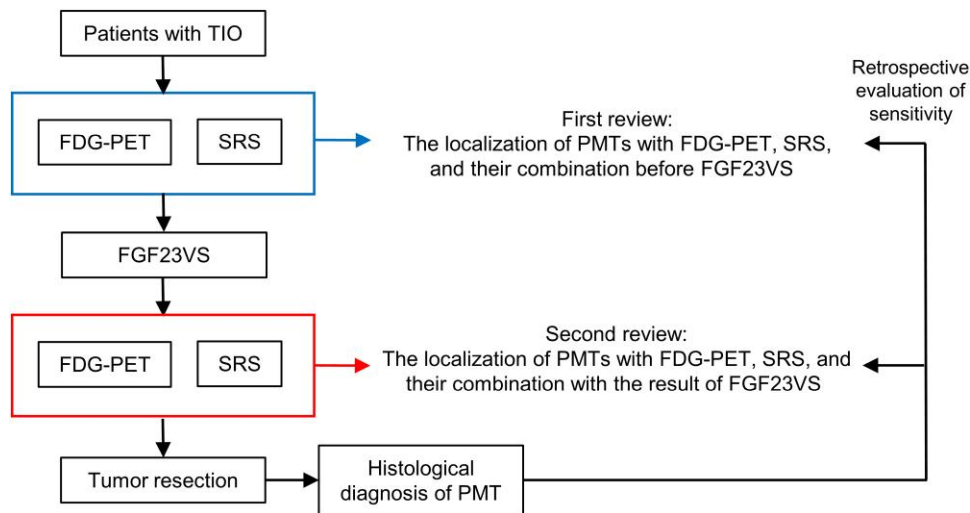
### **Definition of Successful Localization With FDG-PET, SRS, and FGF23VS**

In the present study, we only evaluated the sensitivity of FDG-PET, SRS, and FGF23VS among patients with histologically confirmed PMTs, because pathogenesis of patients without identified PMTs might be other causes such as late-onset hereditary FGF23-related hypophosphatemia.

The localization of PMTs with FDG-PET and SRS was regarded as successful when a tumor identified by each study was positive for FGF23 by immunohistochemistry. As stated above, the radiologist reviewed FDG-PET and SRS before FGF23VS (the first review) and after FGF23VS (the second review). Therefore, the successful localization of PMTs by FDG-PET and SRS occurred before or after FGF23VS. The localization of PMTs with FGF23VS was regarded as successful when a sampling site with the highest FGF23 value was located proximally adjacent to the histologically confirmed PMTs. Sensitivity for the localization of PMTs among patients with histological diagnosis of PMTs was calculated for the first and second FDG-PET review, the first and second SRS review, FGF23VS, combinations of 2 tests (the first FDG-PET review and the first SRS review, the second FDG-PET review and the second SRS review, the second FDG-PET review and FGF23VS, and the second SRS review and FGF23VS), and all 3 tests (combination of the second FDG-PET review, the second SRS review, and FGF23VS) (Fig. 1). When the tracers accumulated in sites other than where the responsible tumors were detected among patients with diagnosed PMTs, these accumulations were categorized as “nonspecific.”

### **Genetic Analyses for Patients With Negative Tumor Location**

Genetic analyses were performed in the patients without identified tumors by FDG-PET, SRS, and FGF23VS to exclude the possibility that they were hereditary FGF23-related hypophosphatemias. Genomic DNA was collected from peripheral blood cells using a NucleoSpin blood kit (Macherey-Nagel, Düren, Germany), and whole-genome sequencing was performed by HiSeq X Ten (Illumina, San Diego, CA). Then, exon sequences in the genes responsible for hereditary



**Figure 1.** Flow chart of the retrospective assessment of sensitivity in FDG-PET, SRS, and FGF23VS.

FGF23-related hypophosphatemia (*PHEX*, *DMP1*, *FGF23*, *ENPP1*, *FAM20C*, *FGFR1*, *PTH1R*, *NF1*, *GRAS*, *HRAS*, *NRAS*, *KRAS*) were analyzed. The Genome Aggregation Database [35] and a whole-genome reference panel from 3552 Japanese individuals provided by the Tohoku Medical Megabank Organization [36] were referenced to determine the allele frequencies of the detected variants.

## Results

### Clinical and Biochemical Data of the Patients

At the time of referral to our institute, the median age of the patients was 60 years (range, 28-87), and 33% were women. All patients exhibited hypophosphatemia with a median serum phosphate level of 1.9 mg/dL (1.0-2.5) and inappropriately increased FGF23, with a median serum FGF23 level of 230.5 mg/dL (52.1-5216.0) (Table 1).

### Clinical Outcomes

Tumors were localized and histologically diagnosed as PMTs in 18 (60%) patients (Table 2). The PMTs were located in the skull bone (n=2 [11%]), costal bone (n=1 [6%]), pelvis (n = 6 [33%]), upper limb bone (n=1 [6%]), lower limb bone (n=2 [11%]), adipose tissue in the head and neck (n = 1 [6%]), thoracoabdominal area (n=1 [6%]), pelvic area (n=3 [17%]), and lower limb area (n=1 [6%]). In case 2, although imaging studies suggested a responsible tumor at the acetabulum, surgical resection was not performed due to deterioration of the patient's health status. Among 18 participants with histologically confirmed PMTs who underwent surgery, serum FGF23 and phosphate levels were normalized in 15 (83%) patients. When residual tumors were expected, burosumab injection was initiated in cases 1, 14, and 19.

### Sensitivity of FDG-PET and SRS

The sensitivity of the first FDG-PET review in localizing PMT was 72%, which increased to 89% in the second FDG-PET review (Table 3). While the first FDG-PET review did not achieve successful tumor localization in cases 1, 15, and 26, the second review identified the PMTs in these cases with reviews of the results acquired from FGF23VS. Figure 2

demonstrates how FGF23VS data assisted the tumor localization in the second review of FDG-PET in cases 1, 15, and 26. The levels of sensitivity of the first and the second SRS reviews were both 72%. The sensitivity of the combination of the first FDG-PET and SRS review was 89% and that of the second PET/CT and SRS review was 94% (Table 3, Fig. 3). Nonspecific accumulation of tracers other than PMTs was

**Table 1. Clinical and biochemical data of 30 patients with late-onset FGF23-related osteomalacia**

	Reference range, adults	
Age, years		60 [28-87]
Sex, female (%)		10 (33)
Disease period, months		35 [6-360]
Walking aids (%)		
None		10 (33)
Single cane		0 (0)
Double canes		9 (30)
Walker		0 (0)
Wheelchair		11 (37)
Bedridden		0 (0)
Laboratory data		
Serum P, mg/dL	2.7-4.6	1.9 [1.0-2.5]
Serum albumin-adjusted Ca, mg/dL	8.8-10.4	8.8 [7.6-10.2]
FGF23, pg/mL	Less than 30	230.5 [52.1-5216.0]
1,25(OH) <sub>2</sub> D, pg/mL	20.0-60.0	34 [4.5-102.0]
iPTH, pg/mL	15-65	62 [17-259]
eGFR, mL/min/1.73 m <sup>2</sup>		82.6 [37.0-173.6]
Tmp/GFR (mg/dL)	2.3-4.3	1.36 [0.36-2.14]

Values are reported as medians [range]. Abbreviations, 1,25(OH)<sub>2</sub>D, 1,25-dihydroxyvitamin D; Ca, calcium; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; iPTH, intact parathyroid hormone; P, phosphate; Tmp/GFR, tubular maximum transport of phosphate.

**Table 2. Clinical outcomes of 30 patients with late-onset FGF23-related osteomalacia**

Patient	Age/ sex	Tumor location detected by FDG-PET, SRS, or FGF23VS	Surgery	Complete resection	Pathological diagnosis	Postoperative treatment
1	41F	Maxillary sinus	Yes	No	PMT (bone)	Inorganic phosphate, active vitamin D
2	49F	Acetabulum	No	NA	NA	Burosumab
3	66F	NA	No	NA	NA	Burosumab
4	54M	Palate	Yes	Yes	PMT (bone)	NA
5	65M	NA	No	NA	NA	Active vitaminD
6	61M	NA	No	NA	NA	Inorganic phosphate, active vitaminD
7	28F	NA	No	NA	NA	Inorganic phosphate, active vitaminD
8	69F	Left tibia	Yes	Yes	PMT (bone)	NA
9	61M	Right greater trochanter	Yes	Yes	PMT (bone)	NA
10	82M	Left ischium	Yes	Yes	PMT (soft tissue)	NA
11	46F	Left perineum	Yes	Yes	PMT (soft tissue)	NA
12	67M	Left humerus	Yes	Yes	PMT (bone)	NA
13	39F	NA	No	NA	NA	Inorganic phosphate, active vitaminD
14	66M	Acetabulum	Yes	No	PMT (bone)	Burosumab
15	59M	Left ilium	Yes	Yes	PMT (bone)	NA
16	84F	NA	No	NA	NA	Burosumab
17	38M	NA	No	NA	NA	Inorganic phosphate, active vitaminD
18	44F	Left buttock	Yes	Yes	PMT (soft tissue)	NA
19	80M	Left ischium	Yes	No	PMT (bone)	Burosumab
20	60F	NA	No	NA	NA	Burosumab
21	64M	Left knee	Yes	Yes	PMT (soft tissue)	NA
22	67M	NA	No	NA	NA	Inorganic phosphate, active vitamin
23	71M	NA	No	NA	NA	Burosumab
24	43M	Right 3rd rib	Yes	Yes	PMT (bone)	NA
25	56M	Left pelvis	Yes	Yes	PMT (bone)	NA
26	44M	Right ischium	Yes	Yes	PMT (bone)	NA
27	87M	Right nasal cavity	Yes	Yes	PMT (soft tissue)	NA
28	51M	Extradural region (Th8-10)	Yes	Yes	PMT (soft tissue)	NA
29	55M	Right medial cuneiform bone	Yes	No	No tumor	Burosumab
30	58M	Right pubis	Yes	Yes	PMT (bone)	NA

Resection of the tumor was regarded as “complete resection” when serum phosphate levels were maintained within the normal range for 1 year after the surgery.

Abbreviations: F, female; M, male; NA, not applicable; PMT, phosphaturic mesenchymal tumor; Th, thoracic spine.

identified in 17 patients (94% of patients with diagnosed PMTs) by FDG-PET and in 11 patients (61% of participants with diagnosed PMTs) by SRS (Table 3, Supplementary Tables S1 and S2) [37].

### Sensitivity of FGF23VS

The highest FGF23 value was located proximally adjacent to the histologically confirmed PMTs in 16 patients among 18 patients with a diagnosis of PMTs (Supplementary Fig. S1 [37]). In case 11, among 3 localization studies (FDG-PET, SRS, and FGF23VS), FGF23VS alone achieved successful tumor localization (Fig. 4). The sensitivity for the localization of PMTs was highest (100%) when 2 localization studies (the second FDG-PET review and FGF23VS) were combined (Fig. 3).

### Additional SR-PET/CT

Among 12 patients without histologically confirmed PMTs (Supplementary Table S3 [37]), 5 patients (cases 3, 5, 6, 7,

and 13) were referred to Kyoto University Hospital and underwent <sup>68</sup>Ga-DOTATOC-PET/CT scans. A potential PMT lesion was detected in the right fourth costal bone in case 3, but the patient refused surgery and participated in the clinical trial of burosumab (Fig. 5) [15]. In cases 5, 6, 7, and 13, <sup>68</sup>Ga-DOTATOC-PET/CT scans failed to detect potential PMTs.

### Genetic Analyses in Patients With Negative Tumor Location

Among 12 patients without identified tumors, whole-genome sequencing was performed in 7 patients. Pathogenic variants reported by previous studies or variants with low allele frequencies (less than 0.5%) were not detected in the exon sequences in the genes associated with FGF23-related hypophosphatemia.

### Discussion

In the current study, we retrospectively analyzed 30 patients with late-onset FGF23-related osteomalacia and found that

**Table 3. Results of localizing studies in the 18 patients with PMTs**

Case	Localization by FGF23VS					Localization by FDG-PET		Localization by SRS		Localization by FDG-PET and SRS	
	Avg. FGF23	Max. FGF23	Min. FGF23	Site of max. FGF23 value	Localization	Before FGF23 VS (1st review)	After FGF23 VS (2nd review)	Before FGF23 VS (1st review)	After FGF23 VS (2nd review)	Before FGF23 VS (1st review)	After FGF23 VS (2nd review)
Positive, n					17	13	16	13	13	16	17
Negative, n					1	5	2	5	5	2	1
Sensitivity, % (n/total n)					94	72 (13/18)	89 (16/18)	72 (13/18)	72 (13/18)	89 (16/18)	94 (17/18)
Nonspecific accumulations of tracers, n (%)						17 (94)		11 (61)			
1	395	518.2	267.4	Proximal SVC	Yes <sup>a</sup>	No <sup>d</sup>	Yes	Yes	Yes	Yes	Yes
4	148.8	203.7	124.4	Right internal jugular vein	Yes	Yes <sup>d</sup>	Yes	Yes	Yes	Yes	Yes
8	2886.8	3913.0	2352.0	Proximal left femoral vein	Yes	Yes	Yes	Yes <sup>d</sup>	Yes	Yes	Yes
9	337.5	412.0	292.9	Right common iliac vein	Yes	Yes <sup>d</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	Yes
10	245.9	750.3	201.6	Left internal iliac vein	Yes	Yes <sup>d</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	Yes
11	157.8	259.9	142.6	Left external iliac vein	Yes	No <sup>d</sup>	No	No <sup>d</sup>	No	No	No
12	237.4	2168.4	123.4	Left brachial vein	Yes	Yes <sup>d</sup>	Yes	Yes	Yes	Yes	Yes
14	3113.3	3985.5	2319.5	Distal IVC	Yes <sup>b</sup>	Yes <sup>d</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	Yes
15	182.6	850.9	115.9	Left internal iliac vein	Yes	No <sup>d</sup>	Yes	No	No	No	Yes
18	266.8	439.5	206.6	Left internal iliac vein	Yes	No <sup>d</sup>	No	Yes <sup>d</sup>	Yes	Yes	Yes
19	745.1	1260.3	570.4	Left internal iliac vein	Yes	Yes <sup>d</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	Yes
21	207.2	364.3	161.8	Left external iliac vein	Yes	Yes <sup>d</sup>	Yes	No <sup>d</sup>	No	Yes	Yes
24	176.6	228.3	138.1	Proximal SVC	No	Yes <sup>d</sup>	Yes	No <sup>d</sup>	No	Yes	Yes
25	575.4	855.5	493.1	Left common iliac vein	Yes	Yes <sup>d</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	Yes
26	258.5	347.0	195.3	Distal IVC	Yes	No <sup>d</sup>	Yes	Yes	Yes	Yes	Yes
27	6383	6740.4	5449.3	Right external jugular vein <sup>c</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	Yes	Yes	Yes
28	328.2	553.5	243.4	Azygous vein <sup>c</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	Yes	Yes	Yes
30	186.2	244.6	140.4	Proximal Right femoral vein	Yes	Yes <sup>d</sup>	Yes	No <sup>d</sup>	No	Yes	Yes

Abbreviations: Avg., average; FDG-PET, <sup>18</sup>F-FDG-PET/CT; FGF23VS, systemic fibroblast growth factor 23 venous sampling; IVC, inferior vena cava; Max., maximum; Min., minimum; PMT, phosphaturic mesenchymal tumor; SRS, somatostatin receptor scintigraphy; SVC, Superior vena cava.

<sup>a</sup>Although the maximum FGF23 level was detected at the proximal SVC, there was a significant increase in the FGF23 level at the left internal jugular vein, which led to the detection of the tumor.

<sup>b</sup>Although the maximum FGF23 level was detected at the distal IVC, there was a significant increase in the FGF23 level at the right internal iliac vein, which led to the detection of the tumor.

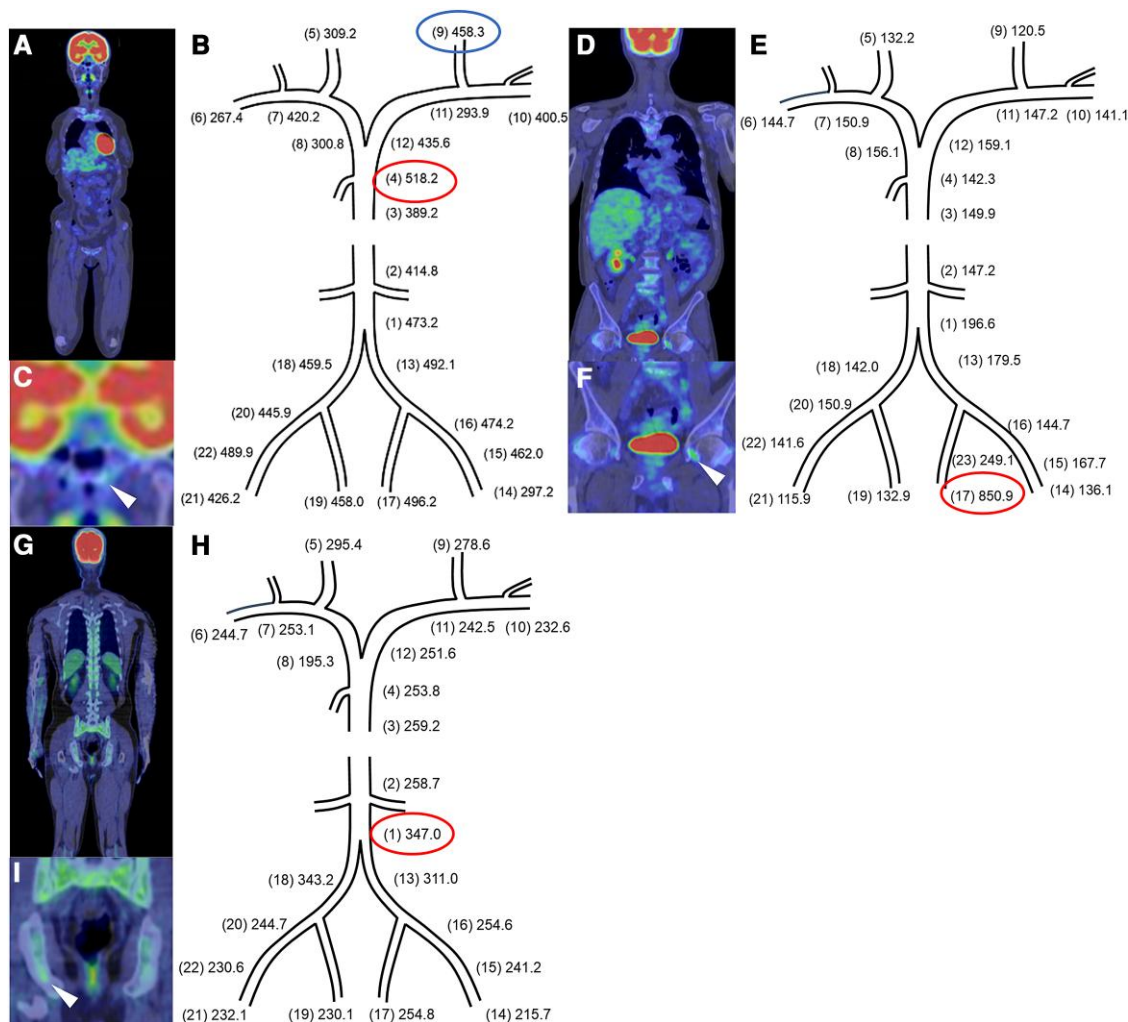
<sup>c</sup>Sampling points were added at the external jugular vein and azygous vein because tumors were suspected near the added sampling points by imaging studies before FGF23VS.

<sup>d</sup>Nonspecific accumulations of tracers were detected in the 1st and 2nd reviews.

the sensitivity for the localization of PMTs among 18 patients with identified tumors reached 100% when 2 localization studies (the second FDG-PET review and FGF23VS) were combined (Table 3, Fig. 3). Without FGF23VS, the sensitivity was increased to 89% by the combination of FDG-PET and SRS (Table 3, Fig. 3).

Since the usefulness of FGF23VS was first introduced by our group [17], several studies have evaluated its diagnostic performance. Because FGF23VS was the only study that could

evaluate both anatomical and hormonal data, the high sensitivity of FGF23VS in detecting PMTs has already been reported. Chong et al reported the high sensitivity (83%) of FGF23VS in 12 patients with histologically confirmed PMTs, the protocol of which resembled that of the current study [29]. Similarly, a relatively high sensitivity (70%) of FGF23VS was reported among 10 patients with suspected TIO from our laboratory in 2010 [18]. In another study, the sensitivity of FGF23VS in detecting the responsible tumors



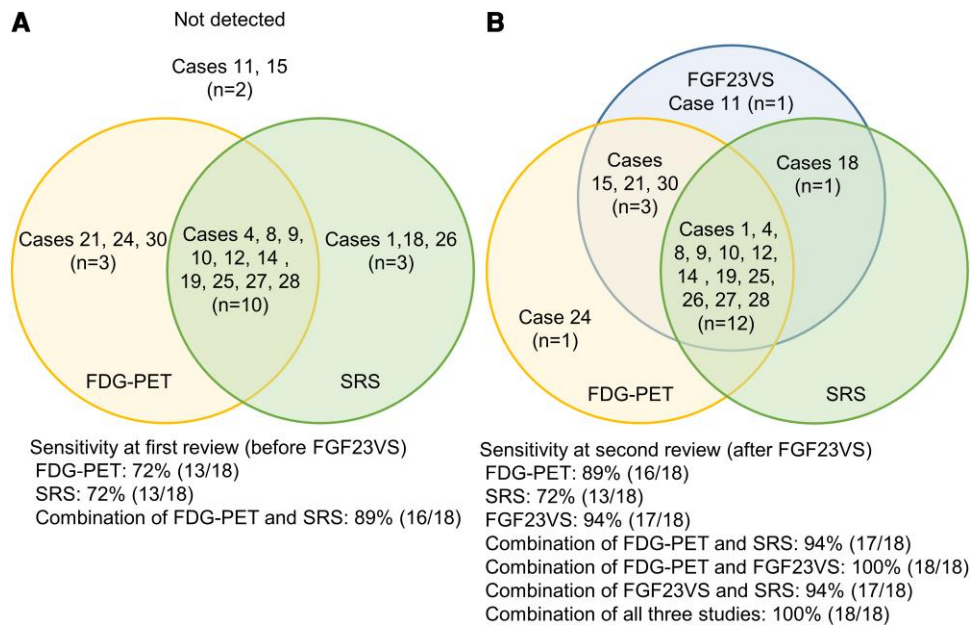
**Figure 2.** FGF23VS complemented the tumor localization by FDG-PET in cases 1, 15, and 26. In the first FDG-PET review (case 1: A; case 15: D; case 26: G), because the accumulations of tracers in PMTs were weak, these accumulations were not classified as possible tumor locations. Then, in case 1, there was a significant increase in the FGF23 level at the left internal jugular vein (blue circle [sampling point 9]) (B), suggesting the tumor location around sampling point 9, while the highest FGF23 level was detected at the proximal SVC (red circle [sampling point 4]), indicating return of the blood from the head through the superficial and azygous vein. Similarly, FGF23VS clarified the highest FGF23 levels around the left internal iliac vein in case 15 (E [sampling point 17]) and the distal inferior vena cava in case 26 (H [sampling point 1]), suggesting the tumor location around the sampling point with high FGF23 levels. In the second FDG-PET review, the accumulations of tracers in PMTs turned positive (case 1: C; case 15: F; case 26: I).

was estimated to be 87% among patients with suspected TIO [28]. These 2 studies might include patients with FGF23-related hypophosphatemic osteomalacia due to etiologies other than TIO [18, 28]. In our case series, the sensitivity of FGF23VS was revealed to be 94%, which was compatible with the above-cited articles. Furthermore, the sensitivity of FGF23VS (94%) was higher than that of the first FDG-PET review (72%), the first SRS review (72%) or the combination of the first FDG-PET review and the first SRS review (89%). Therefore, FGF23VS should be conducted as a routine localization study, if available.

Because FGF23VS could provide both hormonal and anatomical information, FGF23VS was more useful than imaging studies, especially when clinicians needed a high degree of certainty before tumor resection. Nonspecific accumulations of tracers in FDG-PET were detected in 94% of patients with PMTs in the present study, which was reminiscent of a previous study reporting low specificity of FDG-PET (36%) [29]. This is because tracers can accumulate in regions with inflammation and other types of tumors in FDG-PET, which leads to

low specificity of the modality. Moreover, the present study revealed that nonspecific accumulations of tracers in SRS were also high (61%) because uptake in lesions with inflammation, such as pseudofractures, was sometimes detected by SRS [25]. Due to nonspecific accumulations of tracers in FDG-PET (94%) and SRS (61%), these imaging studies alone might not provide sufficient information for the decision of tumor resection, especially when multiple suspicious tumors are detected or suspicious tumors are located at sites where it is difficult for the surgeon to approach the tumor or remove the tumor while preserving skeletal function. Although imaging study followed by biopsy was reported to be useful when the tumor was located at the mandible [38], suspicious tumors sometimes reside in sites where biopsies are difficult to perform, again suggesting the utility of FGF23VS when a high degree of certainty is needed preoperatively.

Our study showed that limiting the sampling point of FGF23VS would not be beneficial even when suspicious tumors were detected using FDG-PET and SRS. As we presented in patients 11 and 15 (Fig. 3A), the first review of the



**Figure 3.** Venn diagram of the results of tumor localization by imaging study. Tumors were not detected by FDG-PET and SRS in 2 cases (case 11 and case 15) before performing FGF23VS (A), combination of FDG-PET, SRS, and FGF23VS localized tumors in all cases (B).

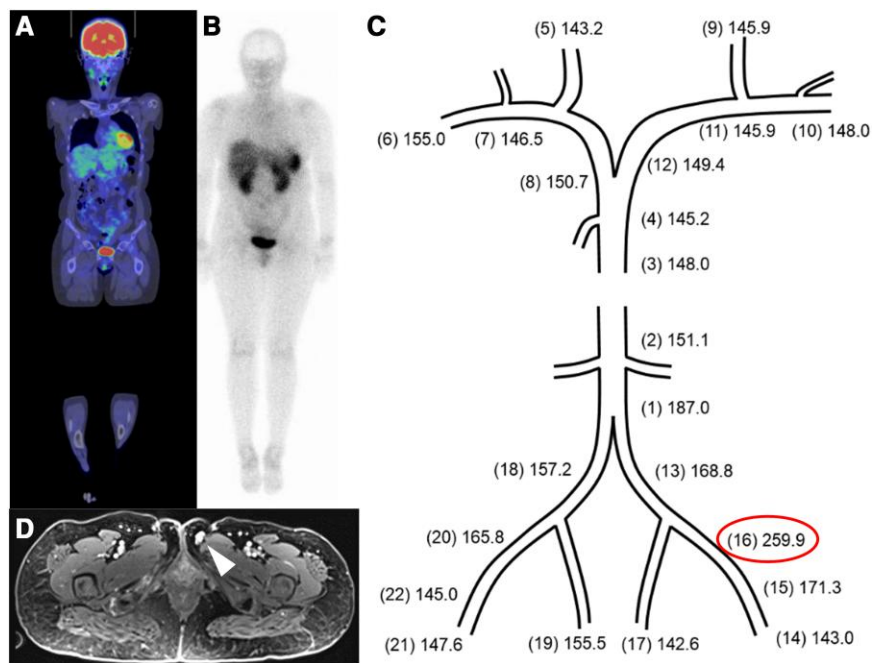
combination of FDG-PET and SRS did not always detect PMTs and provided pleural nonspecific accumulations (Supplementary Tables S1 and S2 [37]). Limiting the sampling points based on the first review of FDG-PET and SRS might decrease the final detection rate. Additionally, collecting blood samples from 22 to 28 veins usually takes 1 to 2 hours for experienced radiologists, as only relatively thick veins were approached without inserting and wedging catheters into thin veins, which also accounts for the very low rates for severe complications such as perforation of the vein. Therefore, limiting the number of sampling points is not predicted to be associated with a significant decrease in the incidence of severe adverse events.

The present study also suggested the benefit of the combination of functional imaging studies. In the current study, the sensitivity of the combination of the first FDG-PET review and the first SRS review (89%) was higher than both of these studies individually (first FDG-PET review: 72% and first SRS review: 72%). Although a detailed comparison of the sensitivity of each functional imaging study and the combination of these studies has not been reported thus far, several articles have suggested the benefit of the combination of functional imaging modalities. In a study with 11 TIO patients reported by El-Maouche et al, in 1 patient, although both SR-PET/CT and SRS were negative, FDG-PET detected PMT [24]. However, in the other 2 patients, both SR-PET/CT and SRS were positive despite the negative FDG-PET results [24]. Furthermore, in an article by Chong et al with 20 patients with TIO, either SR–single photon emission computed tomography (SPECT) or FDG-PET was negative in 3 patients [29]. Moreover, despite the small sample sizes, several studies reported that FDG-PET and SR-PET/CT or SR-SPECT were mutually compensatory for the detection of PMT, suggesting the benefit of the combination of some functional imaging tests [39, 40]. Our present data were compatible with these previous studies and clarified that a better localization rate was achieved when several imaging studies were integrated.

Images obtained by FDG-PET reflect the intake of glucose in the tumor cells; hence, FDG-PET is supposed to be beneficial for identifying rather undifferentiated tumors. However, SRS could be effective in localizing well-differentiated hormone-producing tumors. Therefore, the combination of FDG-PET and SRS could provide an additive effect to detect PMTs, leading to improved sensitivity, and could be a beneficial diagnostic approach for institutes where FGF23VS is not available. Additionally, because our present study showed that the combination of FDG-PET and FGF23VS discovered all identified PMTs (Fig. 3B), SRS can be avoided when FDG-PET and FGF23VS are available.

SR-PET/CT, including  $^{68}\text{Ga}$ -DOTATOC-PET/CT,  $^{68}\text{Ga}$ -DOTANOC-PET/CT, and  $^{68}\text{Ga}$ -DOTATATE-PET/CT, is now superseding SRS and SR-SPECT with better resolution and sensitivity in the identification of neuroendocrine tumors. The utility of SR-PET/CT in searching for PMT was reported by Paquet et al, who revealed a relatively high sensitivity (73%) and specificity (67%) of  $^{68}\text{Ga}$ -DOTATOC-PET/CT in 15 patients with suspected TIO [25]. Additionally, in Japan, the detection rate of  $^{68}\text{Ga}$ -DOTATOC-PET/CT performed at Kyoto University among 35 patients with suspected TIO was reported to be 57% (20/35) [41], which was superior to the detection rate of F-PET/CT (14/30, 47%) and SRS (13/30, 43%) and was similar to that of FGF23VS (18/30, 60%) in the current study when the 12 patients with unidentified PMTs were added to the 18 patients with identified PMTs, as the previous study did. In addition, among patients without identified tumors with FDG-PET, SRS, and FGF23VS, 5 patients (cases 3, 5, 6, 7, and 13) were referred to Kyoto University Hospital to be subject to  $^{68}\text{Ga}$ -DOTATOC-PET/CT, and the accumulation of tracer was identified in case 3 (Fig. 5). The sensitivity of SR-PET/CT was not evaluated in the present study because only 5 of 30 patients (cases 3, 5, 6, 7, and 13) underwent SR-PET/CT. However, it is undoubtable that SR-PET/CT has higher sensitivity and specificity than SRS or SR-SPECT. Moreover, in the present study, the localization rate was maximized (100%) using the





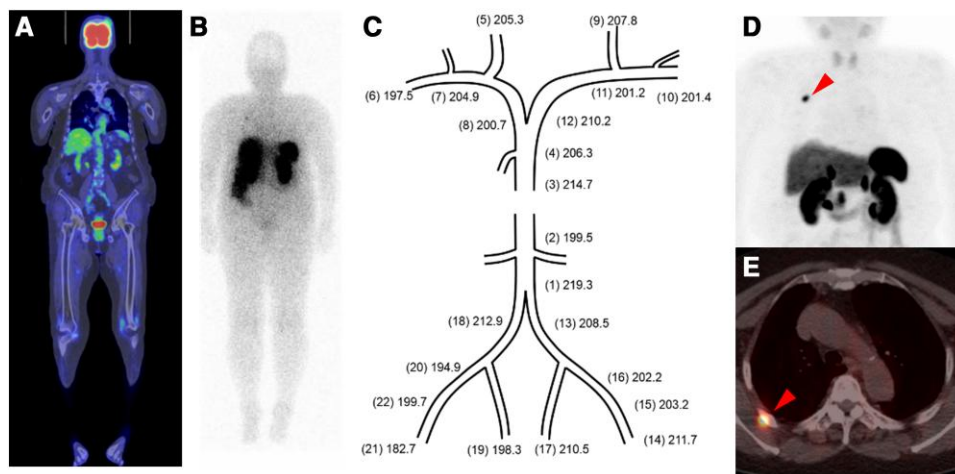
**Figure 4.** FGF23VS localized the responsible tumors in cases with negative tumor detection by FDG-PET and SRS (case 11). While FDG-PET (A) and SRS (B) failed to detect PMT, FGF23VS showed elevation in FGF23 levels around the left external iliac vein (C [sampling point 16]). Enhanced MRI showed PMT around the site where FGF23 was elevated in FGF23VS (arrowhead) (D).

combination of FDG-PET and FGF23VS, suggesting the inferiority of the sensitivity of SRS in detecting PMTs, probably because SRS had lower resolution and sensitivity to detect small tumors compared with SR-PET/CT. However, although the availability of SR-PET/CT is expanding in several nations, it is inaccessible or still limited to the small number of institutions in many countries, and unfortunately, it has not been accessible in Japan until recently.

Medical costs for the localization studies including FDG-PET, SRS, FGF23VS, and SR-PET/CT, are relatively high. Although our study showed that the combinations of these studies would maximize the sensitivity, in the clinical setting, these localization studies should be performed sequentially in order of sensitivity or cost until PMTs are identified to

reduce the burden associated with the medical cost. In the countries where SR-PET/CT is unavailable, we propose that FGF23VS should be routinely performed, if available, before surgery, despite the high cost, especially when PMTs are suspected in cosmetically or functionally important locations, because FGF23VS is the only method available to confirm FGF23 production by the tumor.

The present study has several limitations. First, although SR-SPECT was reported to have a higher sensitivity in localizing PMTs than plain SRS [29], it was not available in our facility. Second, we could not incorporate SR-PET/CT in our analysis of diagnostic performance since only 5 cases underwent SR-PET/CT due to the limited access to SR-PET/CT in Japan. Third, the sensitivity of FGF23VS obtained in the



**Figure 5.** Successful localization of the responsible tumor with SR-PET/CT in Case 3. SR-PET/CT (d, coronal image; e, axial image) localized the responsible tumor (red arrowhead) undetected by FDG-PET (A), SRS (B), and FGF23VS (C).

current study was not comparable with the performance of FGF23VS conducted in other institutions due to the difference in proficiency level among radiologists who performed FGF23VS. Fourth, with the institutional protocol we adopted, FGF23VS was always conducted with extra sampling points around the possible PMTs, if any, detected by previously conducted FDG-PET and SRS, which could inflate the sensitivity of FGF23VS in our facility. Fifth, 12 patients without pathologically confirmed PMTs were excluded from the analysis in the current study; however, there might be unidentified PMTs in the part or all of these 12 patients. Therefore, the sensitivity of those modalities might be overestimated in the current study. Sixth, due to the small sample size ( $n = 18$ ) of the present study, the calculated sensitivities of tumor localization studies might deviate from the actual detection rates, and the sensitivity described for the result might be overestimated.

In conclusion, we analyzed 30 patients with late-onset FGF23-related osteomalacia who underwent 2 different types of nuclear imaging studies (FDG-PET and SRS) and FGF23VS before surgery and found that the combination of FDG-PET and FGF23VS resulted in maximized sensitivity in localizing PMTs among the 18 patients with identified tumors. While SR-PET/CT would be the first choice for the localization of PMTs in the patients with suspected TIO without the identified tumors, with prevailing modalities in countries where SR-PET/CT is easily accessed, the combination of FDG-PET and FGF23VS would be the best alternative combination of the methods for the identification of PMTs in the countries where the access to SR-PET/CT is limited.

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## Disclosures

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## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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