

Importance of Molecular Imaging Characteristics for the Diagnosis and Management of Tumor-induced Osteomalacia

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Abstract

Objective: Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome associated with the overproduction of fibroblast growth factor 23 secondary to phosphaturic mesenchymal tumors (PMT). Our goal was to describe the morphometabolic characterization and histopathological correlation of images obtained from patients with suspected TIO using gallium-68 (68Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate (68GaDOTATATE) positron emission tomography / computed tomography (PET/CT) in a referral center in Argentina.

Methods: A prospective, descriptive study with patients suspected of TIO who were referred to confirm the presence of primary lesions by 68Ga-DOTATATE PET/CT.

Results: Eighteen patients were included (female: 72.22%; median age: 47.5 years [range: 41.5–54]). The median maximum standardized uptake value (SUVmax) was 17.2 (interquartile range: 6.27–30.6). Lesions diagnosed by 68Ga-DOTATATE PET/CT were predominantly localized in the appendicular skeleton. Most patients had one identifiable lesion. Lesions were focal and well-limited in 66.67% of cases. Histopathological data were available for 13 patients. PMT was diagnosed in 61.54% of cases; in this subgroup, 25% had lesions showing ill-defined borders and confirmed bone erosion. A numerically, non-significant higher SUVmax was found in patients with PMT. Also, a trend towards isolated soft tissue involvement was more commonly observed among these patients.

Conclusion: In our patients with suspected TIO evaluated by 68Ga-DOTATATE PET/CT, a greater number of lesions were unique, well-defined, and localized in the appendicular skeleton. Nevertheless, ill-defined borders, including bone erosion, were reported in 25% of patients with confirmed PMTs. 68GaDOTATATE PET/CT is a valuable diagnostic tool for patients with suspected TIO. Further research is warranted.

Keywords: tumor-induced osteomalacia; phosphaturic mesenchymal tumors; 68Ga-DOTATATE; positron emission tomography; computed tomography.

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Introduction

Tumor-induced osteomalacia (TIO), also called oncogenic osteomalacia, is an infrequent but underdiagnosed paraneoplastic syndrome [1]. TIO is characterized by generalized bone pain, loss of muscle mass, and multiple fractures [2], thereby leading to a

poor health-related quality of life. The biochemical pattern of TIO typically includes hypophosphatemia as a result of increased renal phosphate excretion. This alteration is associated with an acquired excess of fibroblast growth factor 23 (FGF-23) from phosphaturic mesenchymal tumors (PMT) [3, 4].

FGF-23 is a major regulator of phosphate homeostasis that acts at the proximal renal tubule by reducing phosphate reabsorption and inhibiting 1- α -hydroxylase [2]. In contrast to X-linked FGF23-mediated hypophosphatemia, complete removal of PMTs in patients with TIO may lead to the normalization of biochemical alterations and bone remineralization [5], thus highlighting the importance of early diagnosis. These tumors are characterized by the expression of somatostatin receptors (SSTR), enabling the use of molecular imaging, including whole-body scintigraphy, positron emission tomography (PET), with an anatomical correlate for computed tomography (CT), or single-photon emission computed tomography (SPECT) [6]. Specifically, the combination of SSTR-based imaging with PET and multislice CT offers higher spatial resolution and whole-body tomographic imaging. Labeling of somatostatin analogs with gallium-68 (68Ga) using 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) leads to the synthesis of 68Ga-DOTA0-Ty3-octreotate (DO-TATATE), which has shown a higher affinity for SSTR subtype 2 [6].

Our objective was to describe the morpho-metabolic characterization of 68GaDOTA-TATE PET/CT scans and their histopathological correlation in patients from a referral center in Argentina.

Materials and methods

Study design

A prospective, descriptive study was conducted in Hospital Universitario CEMIC, a referral center in Buenos Aires, Argentina, from December 2019 to July 2023. The study was conducted on behalf of the TIO Argentine Working Group, conformed by trained physicians who care for patients with this condition since May 2018. Adult patients with clinical and/or biochemical suspicion of TIO who were referred to the Nuclear Medicine Division to confirm the presence of a primary lesion by 68Ga-DOTATATE PET/CT were included. No specific exclusion criteria were considered. Demographic, clinical, and biochemical data were retrieved from all participants before imaging tests.

Imaging technique

All PET/CT studies were performed using a Phillips Healthcare® Gemini 64 ToF scanner (Cleveland, USA), including a whole-body

scan 60 minutes following the intravenous administration of 106.6 ± 22.2 MBq of 68Ga-DOTATATE. Low-dose CT was used for anatomic characterization and attenuation correction and a 3 minutes for bed position on PET scan.

Coronal, transverse, and sagittal slices were obtained and analyzed visually and semi-quantitatively to calculate the maximum standardized uptake value (SUVmax). All slices were analyzed by two specialists in Nuclear Medicine and two specialists in Imaging Diagnosis to minimize potential biases. Potential disagree was solved by debate among these specialists.

Ethical issues

Written informed consents were obtained from all participants. The study was approved by the CEMIC institutional research committee and by an independent ethics committee (Comité de Ética en Investigación del Instituto Nacional de Psicopatología [CEINAPsi]). The study was carried out in accordance with applicable national regulations in Argentina and the latest version of the Helsinki Declaration.

Statistical analysis

Data were anonymized and tabulated in a Microsoft Excel® spreadsheet. Continuous variables were tested with the Shapiro–Wilk test. Normally distributed variables were expressed as mean $\pm$ standard deviation, while non-normally distributed data were reported as medians and interquartile ranges (IQR). Categorical variables were presented as frequencies and percentages. Missing data were not imputed. Differences between subgroups (patients with PMTs vs. a different histological diagnosis) were evaluated using Chi-square tests for categorical variables. Differences in continuous variables were analyzed using the unpaired t-test or the Mann–Whitney U test, as appropriate. A p value $< .05$ was considered statistically significant. Statistical analyses were performed using SPSS Statistics 20.0.0 for Windows® (IBM Corporation).

Results

Baseline data

Eighteen patients with suspicion of TIO were included. Most of them were female (72.2%) with a median age of 47.5 years (range:

41.5–54). Bone fractures were confirmed in 78.6% of participants and 43.8% of patients were not self-sufficient at the time of 68Ga-DOTATATE PET/CT scans. Median FGF-23 level was 47.5 pg/ml (IQR: 42-54).

Imaging data

The median SUVmax was 17.2 (IQR: 6.3–30.6). Most lesions diagnosed by 68Ga-DOTATATE PET/CT were localized in the appendicular skeleton (46.7%) and in the head and neck (40%). Detailed data is shown in *Figure 1*. The majority of patients (86.7%) had one identifiable lesion (*Figure 2*).

The main imaging characteristics are summarized in *Table 1*. Lesions were focal and well limited in 66.7% of cases; in the remaining 6 patients, lesions had ill-defined borders, suggesting an invasive pattern.

Intravenous CT contrast medium was used in 12/18 subjects (66.7%). Negative PET/TC results were reported in 3 of the remaining 6 participants.

Histological data

Histopathological data were available for 12 patients, after excluding a thyroid lesion considered as a false positive. PMTs were diagnosed in 66.7% of cases ($n = 8$). Four patients had lesions in the limbs, two in head and neck area and two in the axial skeleton. General and histological results are summarized in *Table 2* and *Figure 3*, respectively. In this subgroup of 8 patients with PMTs, 2 (25%) participants had lesions with ill-defined borders, including soft tissue and facial bones involvement.

A numerically, non-statistically significant higher SUVmax and lower bone erosion were found in patients with PMTs. Also, a trend towards the involvement of soft tissue alone ($p = 0.06$, Chi-square test with Yates correction) was more commonly observed among patients with PMTs.

Discussion

In our cohort of patients with suspected TIO who were evaluated by 68Ga-DOTATATE PET/CT, most lesions were unique, well defined, and localized in the appendicular skeleton. Even though statistical analyses should be interpreted with caution considering our small sample size, a distinct subgroup of 25% of all histologically confirmed PMTs of our patients were characterized by images with ill-defined borders, including bone erosions. The proportion of our patients with

invading, lytic lesions is consistent with other case series (Kobayashi et al, Zou et al) [7, 8]. Of note, among our patients with histologically confirmed PMTs, we found a numerically higher SUVmax and a non-significant trend towards adjacent soft tissue involvement.

TIO has been associated with a high burden of disease in terms of fatigue, pain and health-related quality of life [9]; in addition, this disorder is also linked with deleterious effects on bone strength and microarchitecture [10]. Nevertheless, TIO remains an elusive diagnosis due to its insidious initial symptoms and the challenges encountered in the detection of PMTs in soft tissues or bones [6]. Historically, tumors associated with TIO have been described as hemangiopericytomas, giant-cell tumors, and fibromas, among other histological findings [3]. Systematic research led to demonstrate that most of these tumors are a distinct pathologic entity (PMT or mixed connective tissue variant). In the past, diagnostic approaches have relied on physical examination searching for a palpable mass, followed by imaging techniques, including CT or octreotide scintigraphy [6, 11]. Currently, 68Ga-DOTATATE PET/CT represents a better strategy with a higher spatial resolution that allows for faster whole-body scanning. Of note, 68Ga-DOTATATE PET/CT is useful to describe the number and size of lesions, in addition to the presence of bone erosion.

These data may support treatment-related decisions, including surgical and non-surgical interventions. Importantly, surgery is the standard treatment when negative margins can be achieved without significant morbidity [12]. Despite lesions are usually small and benign [13], these tumors may exhibit malignant features with an aggressive clinical behavior [14]. In our cohort, two patients with histologically confirmed PMTs presented poorly-defined borders, with soft tissue and facial bones involvement. In addition, one subject developed secondary, bilateral lung lesions. Of note, radical resection is an effective treatment for the removal of these tumors in patients with lesions located in soft tissues [14]. The confounding clinical manifestations that often contribute to the delayed diagnosis of PMTs can eventually lead to the development of distant metastases. Based on previous research, the accurate diagnosis of PMTs is foundational to clinical cure; with this goal, the selection of 68Ga-

DOTATATE PET/CT as the imaging technology of choice may guide the localization and qualitative diagnosis of lesions [14]. The presence of several lesions may strongly influence PMT management so as to consider other non-surgical strategies, including pharmacological treatment with vitamin D, calcium agents, and FGF-23-targeted drugs. While surgical removal of isolated lesions may be curative, the identification of multiple lesions using 68Ga-DOTATATE PET/CT leads us to hypothesize that surgery may not be a first-line treatment option, since complete resection is impossible due to the unfeasibility of complete removal. PMT, as a functional neoplastic tissue, may only be identified by its characteristic molecular expression without morphological alterations.

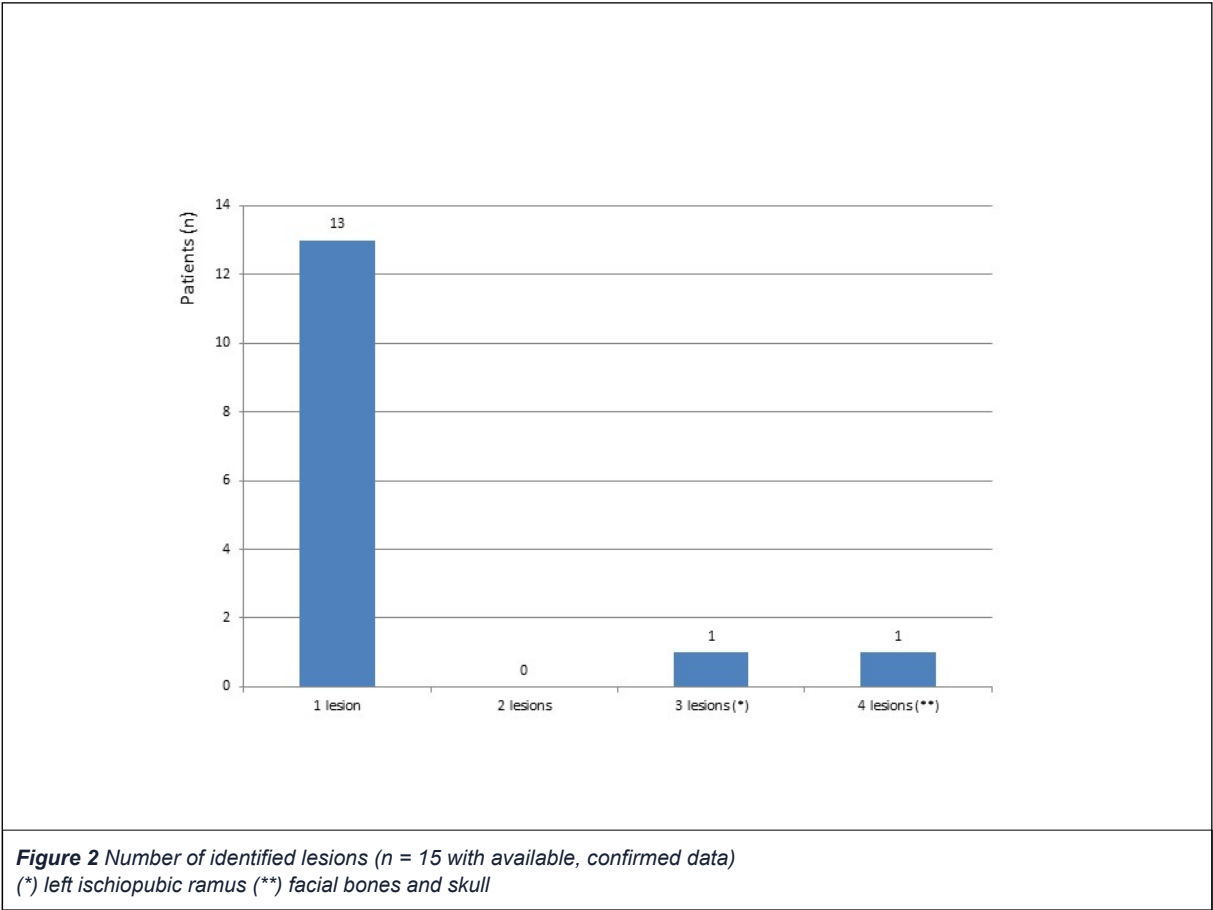
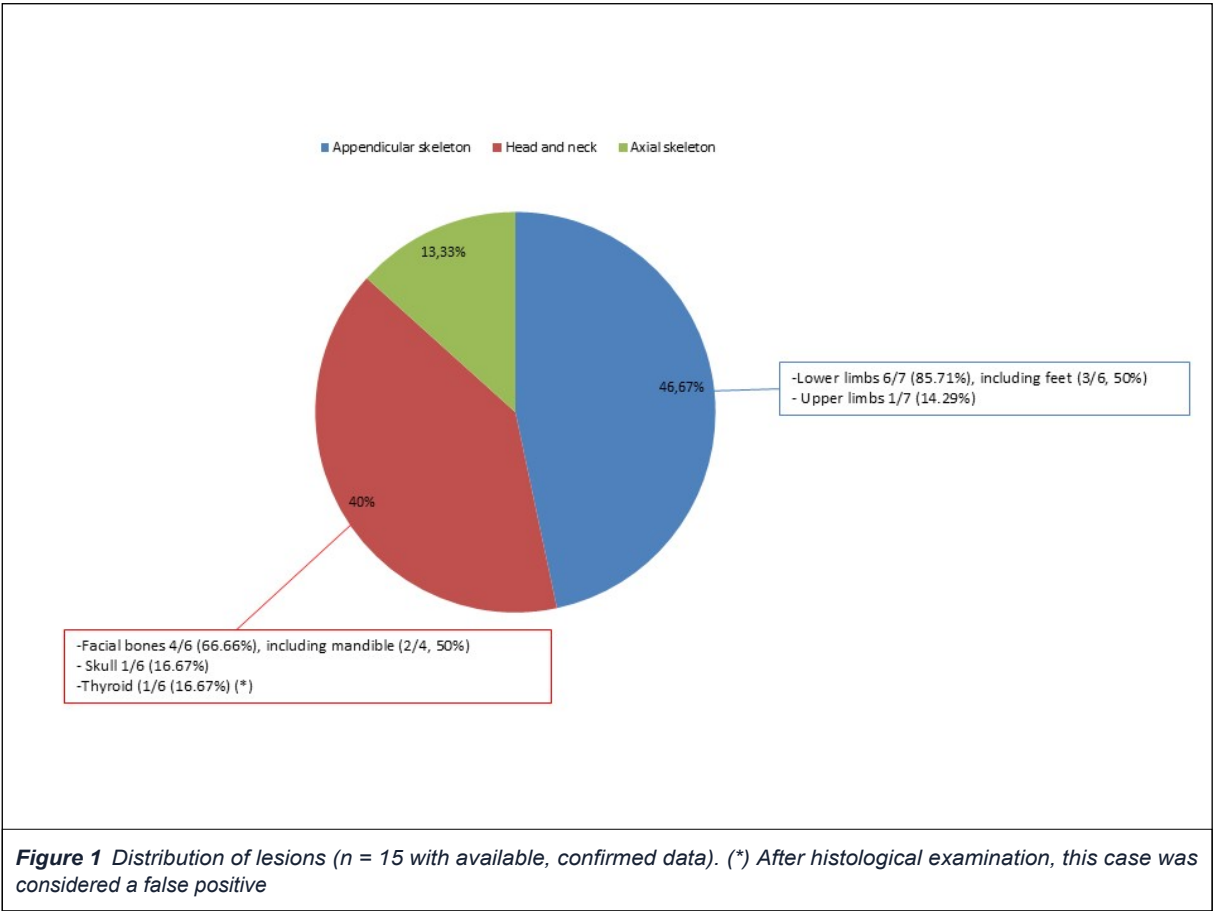
Therefore, in addition to the higher risk of disease recurrence, the proper delimitation of tumor extension may not be viable. 68Ga-DOTA-TATE PET/CT may not only help determine the topographical localization of PMTs, but may also add valuable information to select the best treatment option in case of expansive lesions.

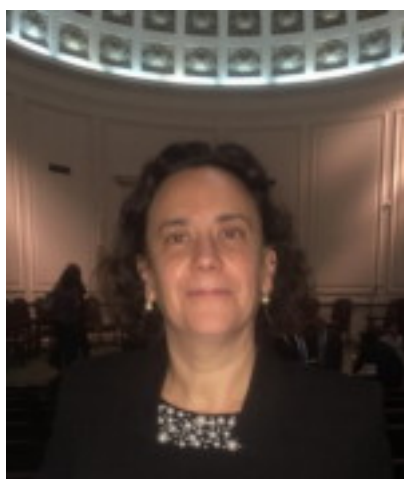
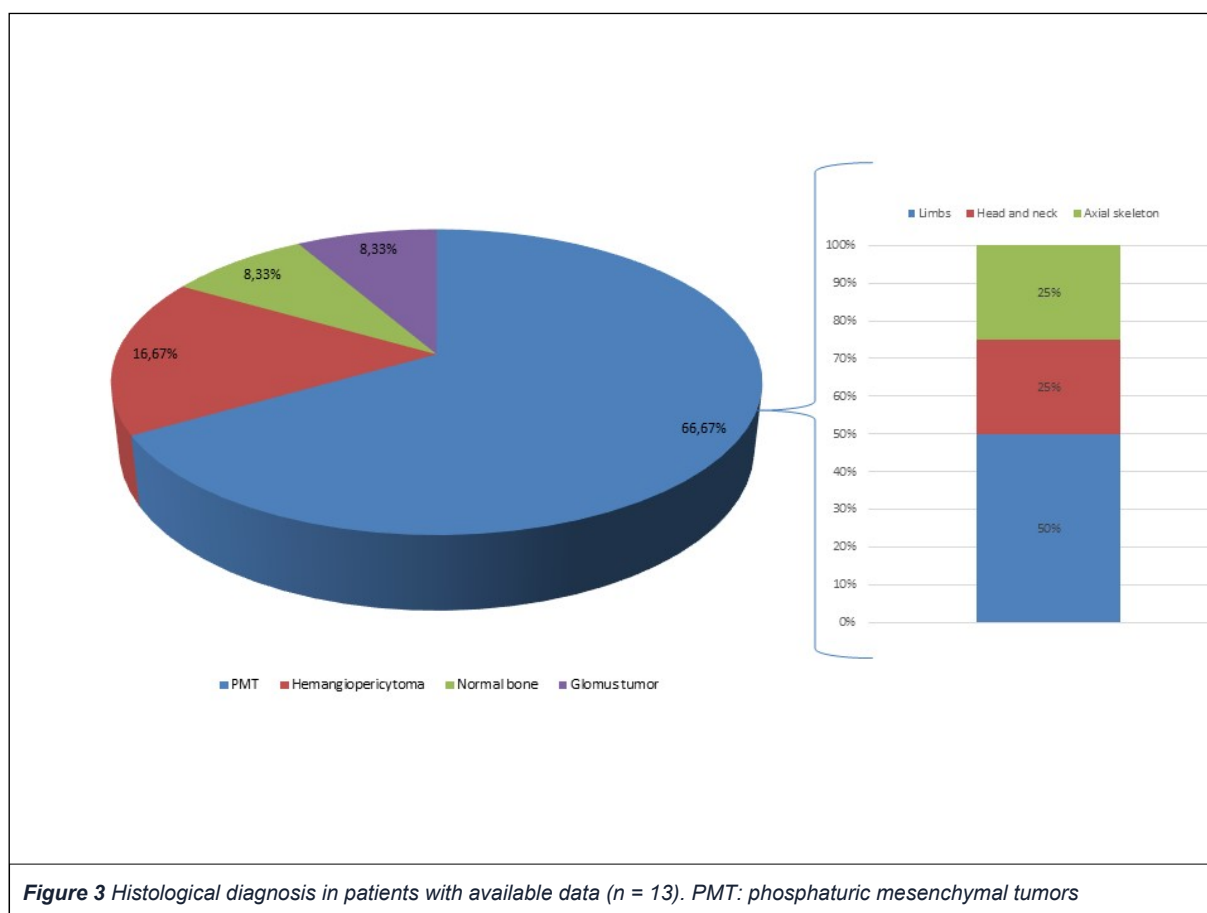
While our research has several limitations, such as the relatively small sample, there are also several strengths: firstly, even though only 18 subjects were enrolled, this sample is highly representative of the general population with TIO in Argentina, according to its reported prevalence [15]. Secondly, the risk of potential biases was reduced by ensuring the central analysis of data, the use of a single PET/CT scanner, and the participation of highly-skilled observers for scan reading. Thirdly, histological data were available for a better characterization of our patients. Fourthly, FGF-23 determinations were available for all subjects, with median levels that might be considered as inappropriately normal, as previously described [16].

We conclude that, in patients with suspected TIO, most lesions were unique, well defined, and localized in the appendicular skeleton according to 68GaDOTATATE PET/CT. Our research adds local evidence to the growing field of using 68Ga-DOTATATE PET/CT as valuable diagnostic tool for patients with suspected TIO. Further research is warranted.

Table 1 Summary of imaging characteristics	
n	18
Transverse diameter, median (IQR)	14 mm (11–23.5)
Long axis, median (IQR)	17 mm (10–18)
Intravenous contrast enhancement, %	66.67%
Tissue involvement, % (*)	
Bone (only)	35.7%
Soft tissue (only)	35.7%
Mixed	21.4%
Visceral	7.2%
Bone erosion, %	50%
CT suggesting osteopenia, %	83.3%
(*) Data available for 14 patients CT: computed tomography; IQR: interquartile range	

Table 2 Characteristics of patients with confirmed PMTs vs. a different histological diagnosis		
	PMT	Other histological findings
n/N	8/13 (61.5%)	5/13 (38.5%)
Female gender, %	75%	60%
Age, median (IQR)	45 years (41–51)	47 years (41–55)
SUVmax, median (IQR)	20.85 (12.4–25.7)	8.3 (4.6–42.5)
Lesion site		
Appendicular skeleton	50%	60%
Head and neck	25%	40%
Axial skeleton	25%	0%
Lesion transverse diameter (median, IQR)	15 mm (12–21)	13.5 mm (11–18)
Lesion long axis (median, IQR)	17 mm (11.5–17.5)	17 mm (13–17.5)
Contrast enhancement	62.5%	80%
Bone erosion	37.5%	80%
CT suggesting osteopenia	75%	80%
Bone fractures	83.7%	50%
Only soft tissue involvement	71.4%	0%
(*) Data available for 6 subjects CT: computed tomography; IQR: interquartile range; PMT: phosphaturic mesenchymal tumor; SUVmax: maximum standardized uptake value		





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Declarations

Consent for publication: The authors clarify that written informed consent was obtained and the anonymity of the patient was ensured. This study submitted to Swiss J. Rad. Nucl. Med. has been conducted in accordance with the Declaration of Helsinki and according to requirements of all applicable local and international standards.

- Competing interests: No competing interests.
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- Consent for publication: Informed consent taken
- Availability of data and materials: The datasets generated during the current study are available from the corresponding author on reasonable request.

Authors' contributions:

MB contributed to the study conception and design. Material preparation and analysis were performed by MB, RC, and MC. Data collection was performed by MB and BZ. The first draft of

the manuscript was written by MB and all authors commented on previous versions of the manuscript. All authors have read and approved the final version of the manuscript.

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