Medical and Surgical Management of Tumor Induced Osteomalacia (TIO)

Bone Day at the University of Kentucky
Friday, Nov 13, 2026

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Disclosures

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Educational Need/Practice Gap

Gap = little, if any education is given on TIO during residency and fellowship; this has led to a significant gap in diagnosing and treating patients with TIO.

Need = to educate clinicians on TIO

Objectives

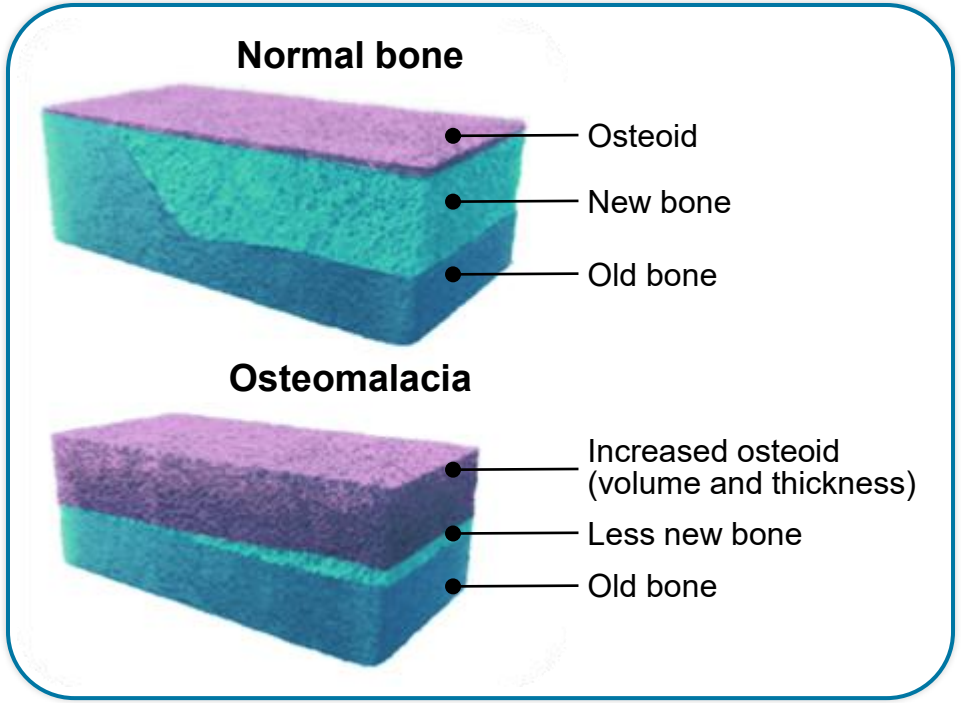
- Review the pathophysiology of tumor-induced osteomalacia (TIO)
- Discuss the current medical and surgical treatment of TIO
- Highlight future research on TIO

Expected Outcome

- What is the desired change/result in practice resulting from this educational intervention? This presentation will hopefully result in earlier diagnosis, treatment, and care of patients with TIO.

Osteomalacia is characterized by impaired bone mineralization resulting in the accumulation of osteoid[1,2]

Osteomalacia, or bone softening, is characterized by accumulation of unmineralized bone matrix (or osteoid) and impaired new bone formation[1,2]



Histomorphometric changes in osteomalacia

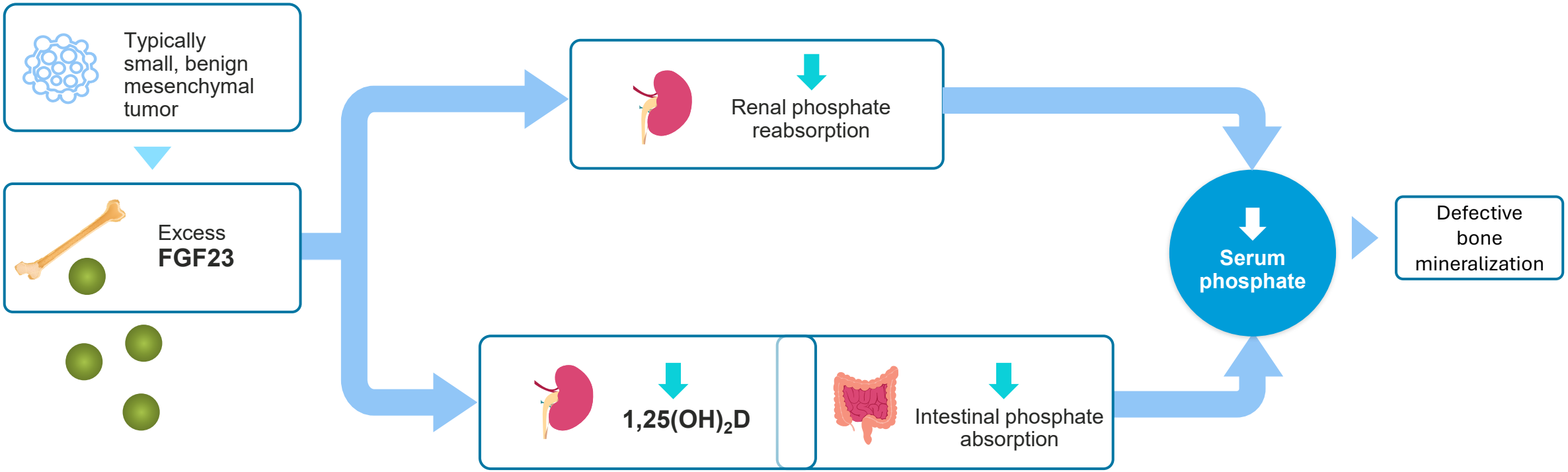
>10% — **INCREASED OSTEOID[3]**
>10% osteoid in the cancellous bone area (normal: <4%)

>15 µm — **INCREASED OSTEOID WIDTH[3]**
Osteoid width >15 µm (normal: 4-12 µm)

>100 days — **DELAYED TIME TO MINERALIZATION[3]**
>100 days (normal: 9-20 days)

1. Parfitt AM. Osteomalacia and related disorders. In: Avioli LV, Krane SM, eds. *Metabolic Bone Disease and Clinically Related Disorders*. 3rd ed. Academic Press; 1998:327-386. 2. Bhan A, et al. *Bone Rep*. 2018;8:125-134. 3. Arboleya L, et al. *J Clin Med.* 2023;12(7):2714.

TIO is an acquired form of hypophosphatemia caused by excess FGF23 produced by tumors[1-3]



$1,25(OH)_2D$, 1,25-dihydroxy vitamin D (calcitriol); FGF23, fibroblast growth factor 23; TIO, tumor-induced osteomalacia.

1. Dahir K, et al. *J Endocr Soc*. 2021;5(9):bvab099. 2. Jan de Beur SM. *JAMA*. 2005;294(10):1260-1267. 3. Jan de Beur SM, et al. *J Intern Med*. 2023;293(3):309-328.

Why should rheumatologists care about TIO?

The most common symptoms of TIO are[1-3]



Bone pain



Fractures/
pseudofractures



Local lumps



Difficulty walking



Height loss



Muscle weakness



Spinal deformity



Thoracic deformity



Tooth loss or
loose teeth

Patients may present with any combination of symptoms that overlap with various musculoskeletal ailments and rheumatologic or neurologic disorders[3]

TIO, tumor-induced osteomalacia.

1. Jan de Beur SM, et al. *J Intern Med*. 2023;293(3):309-328. 2. Feng J, et al. *Endocr J*. 2017;64(7):675-683. 3. Dahir K et al. *J Endocr Soc*. 2021;5(9):bvab099.

Patients with TIO may interact with multiple specialists prior to diagnosis[1-4]



Multidisciplinary management of TIO-related symptoms may be needed for as long as tumors are present

TIO, tumor-induced osteomalacia.

1. Chong WH, et al. *Endocr Relat Cancer*. 2011;18(3):R53-R77. 2. Minisola S, et al. *Nat Rev Dis Primers*. 2017;3:17044. 3. Dahir K, et al. *J Endocr Soc*. 2021;5(9):bvab099. 4. Jan de Beur SM, et al. *J Intern Med*. 2023;293(3):309-328.

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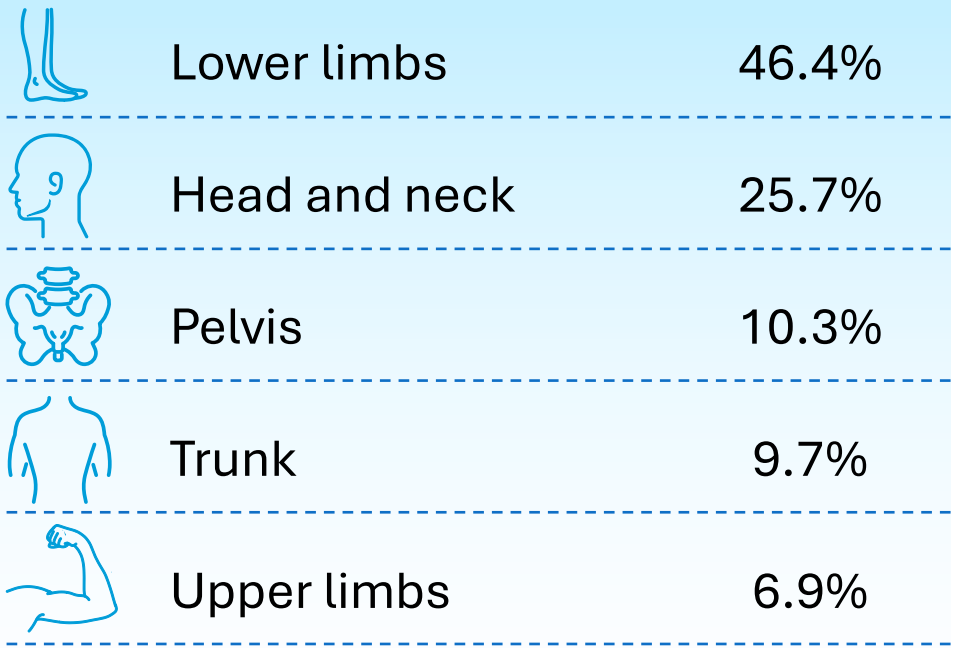
Tumor size can pose a challenge for diagnosing, locating, and successfully resecting the tumor[1,2]

Tumors associated with TIO:

- Often benign and slow growing[2,4]
- Produce FGF23[2]
- Size may be as small as 0.5 cm^3[3]
- Typically appear in adulthood[4]
- Frequently found in the lower extremities, but may occur anywhere in the body[5]

TIO can be cured if the causative tumor is found and completely removed[4,5]

In a systematic review of 895 cases of TIO, prevalence of tumors in the following 5 regions[3]



FGF23, fibroblast growth factor 23; TIO, tumor-induced osteomalacia.

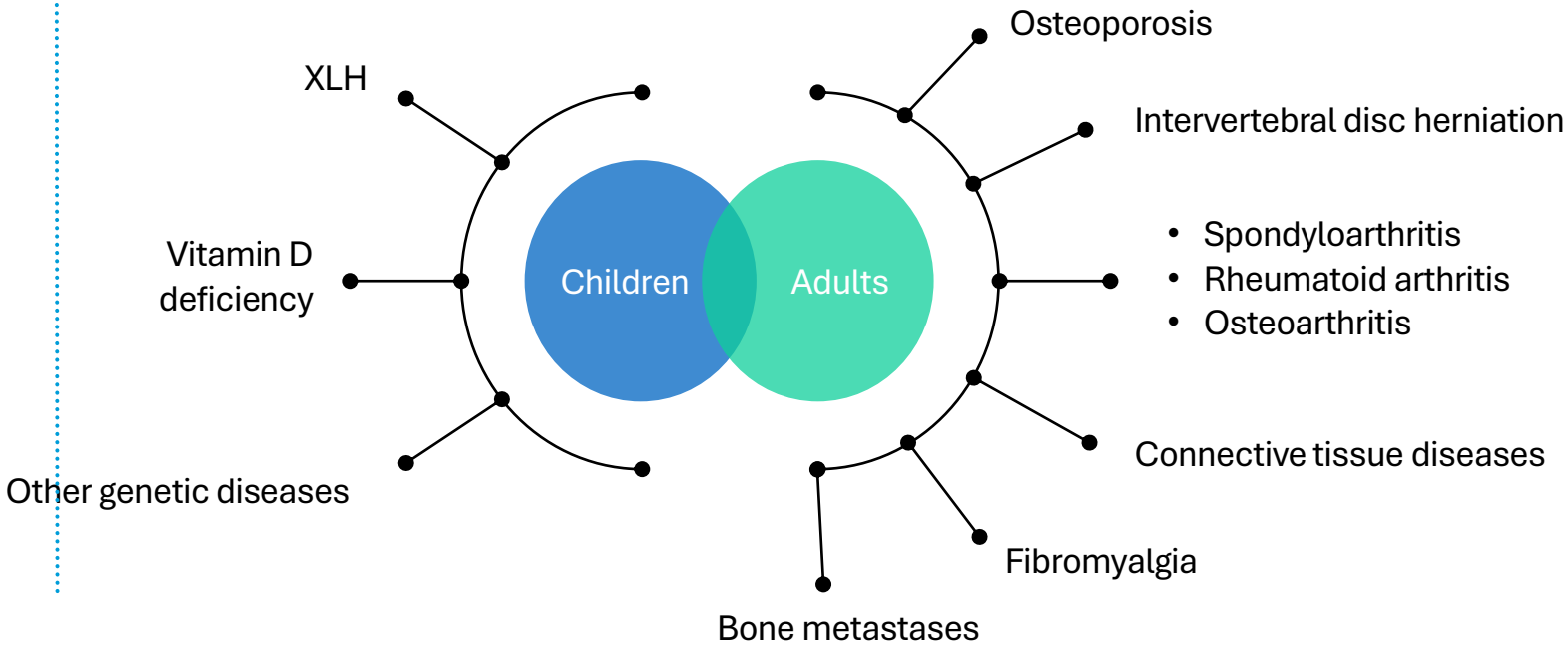
1. Feng J, et al. *Endocr J*. 2017;64(7):675-683. 2 Chong WH, et al. *Endocr Relat Cancer*. 2011;18(3):R53-R77. 3. Bosman A, et al. *Calcif Tissue Int*. 2022;111:367-369. 4. Ruppe MD, Jan de Beur SM. In: Rosen CJ, et al, eds. *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism.* 8th ed. John Wiley & Sons, Inc; 2013. 5. Dahir K, et al. *J Endocr Soc*. 2021;5(9):bvab099.

The path to diagnosis of TIO is lengthy and characterized by frequent misdiagnoses[1]

A retrospective cohort study of 144 TIO patients found that[1]:

- **Up to 95% of patients with TIO are misdiagnosed**[1]
- **Average time to accurate diagnosis is around 3 years** from time of symptom onset[1]

Potential misdiagnoses for patients with TIO can include[1,2]



Full-body functional imaging is key to identifying and locating tumors responsible for TIO[3]

TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemia.

1. Feng J, et al. *Endocr J*. 2017;64(7):675-683. 2. Dahir K, et al. *J Endocr Soc*. 2021;5(9):bvab099. 3. Jan de Beur SM, et al. *J Intern Med*. 2023;293(3):309-328.

Considerations for TIO management



Identification of location of tumor via physical examination and imaging



Surgical resection if possible



Nonsurgical management may be necessary



Management of TIO-related symptoms

TIO, tumor-induced osteomalacia.

Minisola S, et al. *Nat Rev Dis Primers*. 2017;3:17044.

TIO management

Localization precedes any intervention. Because PMTs are typically small (2–3 cm), slow-growing, and can arise anywhere in bone or soft tissue, functional imaging — preferentially **68Ga-DOTATATE PET/CT** (exploiting SSTR2 overexpression, sensitivity 55–100%, specificity 86–100%) — is the first-line study, followed by anatomic CT/MRI of suspicious areas. [2][5]

Selective venous sampling for FGF23 is reserved for discriminating among multiple suspicious lesions or confirming that an identified lesion is the culprit before morbid surgery. [2][6] The following algorithm from the Nature Reviews Disease Primers on TIO summarizes this stepwise localization-to-treatment pathway:

Evaluation of Tumor-Induced Osteomalacia with ^{111}In-Pentetreotide Scintigraphy

Fathima Fijula Palot Manzil, Pradeep G. Bhambhvani, and Janis P. O'Malley

Division of Nuclear Medicine, Department of Radiology, University of Alabama at Birmingham, Birmingham, Alabama

In cases of nonhereditary osteomalacia associated with hypophosphatemia and inadequate response to vitamin D supplementation, one should consider the possibility of tumor-induced osteomalacia, a paraneoplastic syndrome caused by small mesenchymal tumors often found in obscure locations. We present a case of tumor-induced osteomalacia in which ^{111}In-pentetreotide scintigraphy aided in accurate localization of the culprit brachial plexus tumor and cure after resection.

Key Words: tumor-induced osteomalacia; ^{111}In-pentetreotide scintigraphy; somatostatin receptors

J Nucl Med Technol 2013; 41:299–301
DOI: 10.2967/jnmt.113.126763

units/L; reference range, 39–117 units/L), undetectable 1,25-dihydroxyvitamin D (<8 pg/mL; reference range, 18–92 pg/mL), and a decreased level of serum phosphorus (1.3 mg/dL; reference range, 2.4–5 mg/dL). Fibroblast growth factor 23, key to pathogenesis of tumor-induced osteomalacia, was also elevated (320 relative units/mL; reference range, ≤180 relative units/mL). A planar 4-h whole-body ^{99m}Tc-methylene diphosphonate (22 mCi) bone scan suggested osteomalacia (Fig. 1). Because tumors causing tumor-induced osteomalacia may express somatostatin receptors, ^{111}In-pentetreotide (223.5 MBq [6.04 mCi]) scintigraphy was done 24 h after radiotracer administration. Planar and SPECT images (Fig. 2) revealed focal uptake in the right axilla, which correlated with a well-circumscribed lesion within the

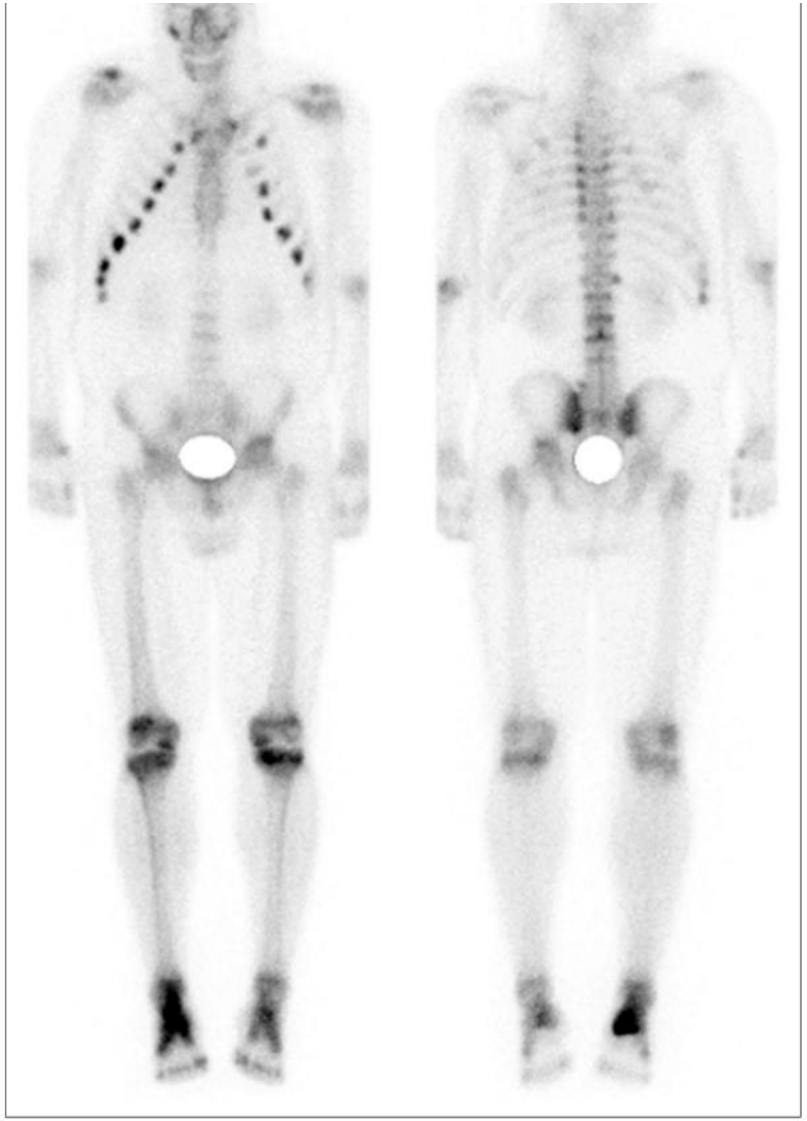


FIGURE 1. ^{99m}Tc-methylene diphosphonate bone scan reveals rosary-bead pattern of uptake at costochondral junctions suggestive of osteomalacia or other metabolic bone disease. Uptake related to right calcaneal fracture and subacute compression fractures of upper lumbar vertebrae are also evident.

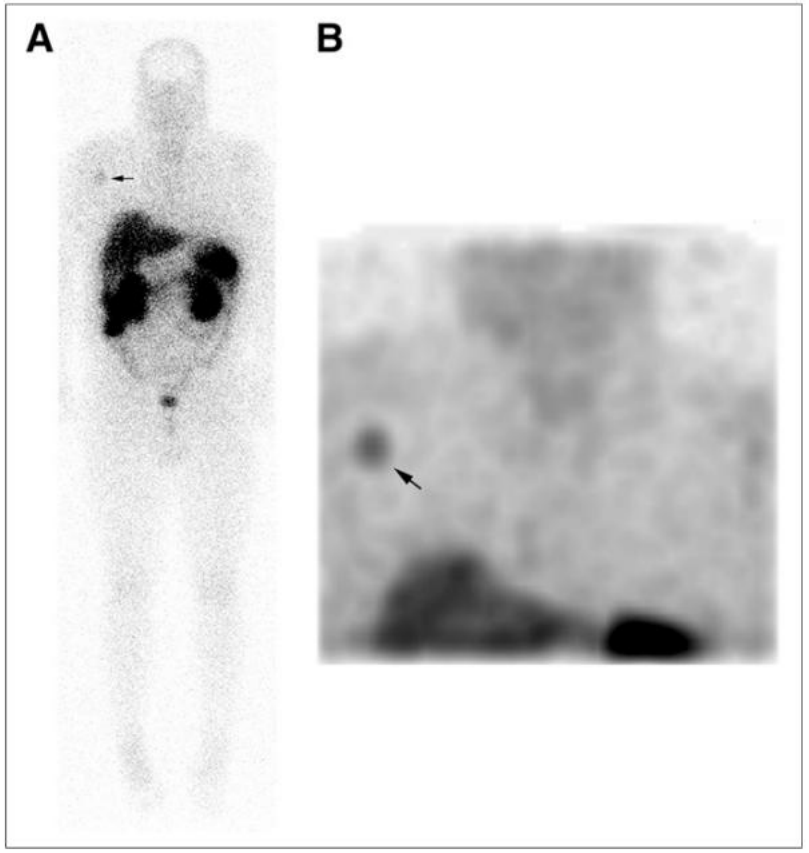
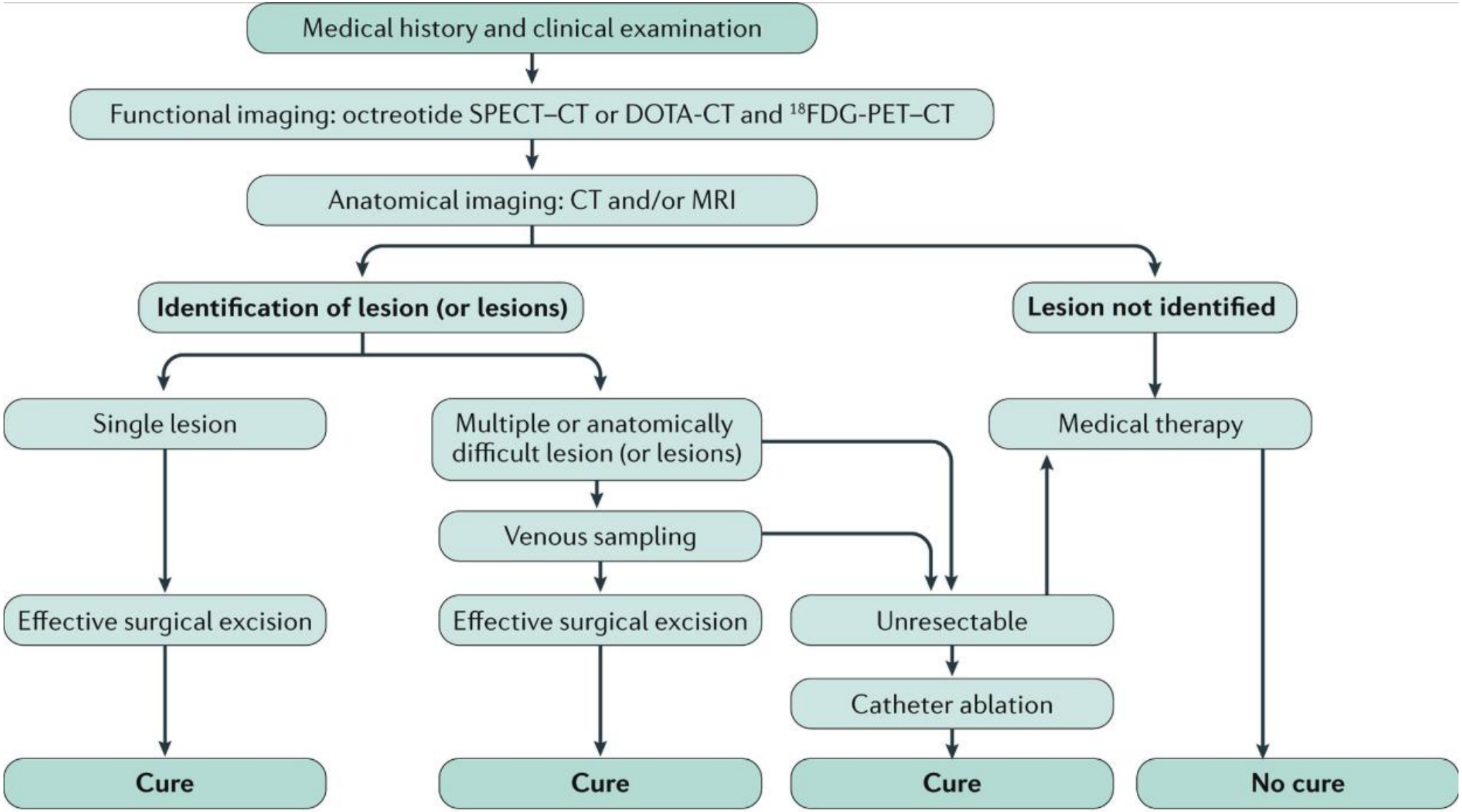


FIGURE 2. ^{111}In-pentetreotide planar (A) and SPECT (B) images acquired 24 h after radiotracer injection depict focal uptake within right axilla.



FIGURE 3. Contrast-enhanced coronal CT scan of chest shows well-defined lesion in proximal right coracobrachialis muscle.

J Nucl Med Technol 2013; 41:299–301 DOI: 10.2967/jnmt.113.126763



Nature Reviews | Disease Primers

Surgical management

Wide en bloc excision with negative margins is the standard and the only reliably curative approach. In a systematic review of >1725 cases, tumors were identified in 1493 patients and surgery was successful in >90% of them. Real-world cure rates are lower — roughly 58–67% after initial surgery in a large multinational review, reflecting incomplete resection and difficulty in localization. [1][8]

Complete surgical resection with wide, negative margins is the definitive, curative treatment for TIO, and it should be pursued whenever the causative phosphaturic mesenchymal tumor (PMT) can be localized and safely removed. [1-3].

Surgical management

Marginal/intralesional resection risks persistence and recurrence.

Positive margins predict persistent or recurrent disease; ~11% of tumors persist and ~7% recur after surgery in retrospective series. In a 117-patient cohort, bone-derived tumors, younger age, malignant histology, and tumors of the femoral head, acetabulum, and spine carried the highest non-remission and recurrence risk. [2][6][9]

Surgical management

Biochemical confirmation of cure is rapid.

Serum FGF23 falls within a day and serum phosphate normalizes within about 7 days in most cured patients. Anticipate and manage **hungry bone syndrome (HBS)** and post-operative hypocalcemia/secondary hyperparathyroidism in the recovery period. [1][9]

Surgical management

Image-guided ablation (for non-surgical candidates or persistent disease)

- **Radiofrequency ablation or cryoablation** are effective alternatives when surgery is not feasible or has failed, with successful biochemical and symptomatic resolution reported in case series. Ablation should extend well beyond the radiographic margin to prevent recurrence. [5-6][10-11]

Medical Management

- When the tumor cannot be located, cannot be resected, or recurs, management shifts to image-guided ablation and/or medical therapy — with the anti-FGF23 monoclonal antibody **burosumab** now the preferred pharmacologic option and **oral phosphate plus active vitamin D (calcitriol/alfacalcidol)** as the conventional alternative. [1-2] Biopsy of a suspected PMT is generally discouraged because of the risk of cell spillage and subsequent recurrence. [4]

Medical Management

Therapy	Regimen/Key Points	Caution/Monitoring
Burosumab (anti-FGF23 mAb)	FDA-approved for FGF23-related hypophosphatemia in TIO not amenable to resection (age ≥2). Adult TIO: 0.5 mg/kg every 4 weeks (titratable); pediatric TIO: 0.4 mg/kg every 2 weeks (max 180 mg). Discontinue oral phosphate/active vitamin D ≥1 week before starting. Restores serum phosphate and improves osteoid parameters, fracture healing, pain, and function.	FGF23 assays cannot be interpreted during therapy (cannot distinguish bound vs free). Frequent but usually mild adverse events; monitor for hyperphosphatemia.
Conventional therapy (oral phosphate + vitamin D; calcitriol/alfacalcidol)	Phosphate ~15–60 mg/kg/day in 4–5 divided doses plus calcitriol ~15–60 ng/kg/day divided; never use phosphate alone. Reasonable initial approach while localizing tumor / awaiting surgery.	Narrow therapeutic window, GI intolerance, nephrolithiasis, nephrocalcinosis, and secondary/tertiary hyperparathyroidism. Check serum Ca, phosphate, PTH, and urine Ca every ~3 months.
Cinacalcet (adjunct)	Calcimimetic that lowers PTH and raises phosphate reabsorption; some benefit but requires further study in TIO.	Risk of hypocalcemia and worsening hypercalciuria; monitor urine calcium and consider adding a thiazide.
FGFR inhibitors	For rare malignant/metastatic PMTs. Infigratinib was studied for unresectable PMT but the trial was terminated (ocular toxicity, failed primary endpoint) and the drug has since been withdrawn.	Experimental; reserved for malignant disease.

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Medical Management

- **Long-term surveillance is mandatory** given the risk of local recurrence and (rarely) metastasis; recurrences have been noted particularly in patients who underwent prior closed biopsy. [4][9]

- The goals are to relieve symptoms, restore phosphate homeostasis, normalize alkaline phosphatase and PTH, and heal osteomalacia; neither burosumab nor conventional therapy halts tumor growth.

Medical Management:
Take home messages

- **Start therapy at biochemical diagnosis** — even before or while awaiting surgery — to heal osteomalacia and prepare the skeleton, which may also reduce post-operative HBS. Case data suggest burosumab can be used pre-operatively to mitigate HBS/hyperparathyroidism after resection. [1][18]

- **Preference for burosumab over conventional therapy** in unresectable/nonlocalizable disease is supported by phase 2 trial and meta-analytic data showing durable phosphate normalization, improved histomorphometry, and pain reduction, with an acceptable safety profile — though head-to-head comparative and long-term data remain limited. [1][14-15]

- **Malignant or metastatic PMT** (rare) requires oncologic management with resection where possible and consideration of targeted/systemic therapy; these cases carry the worst prognosis.

TIO in a hand lesion

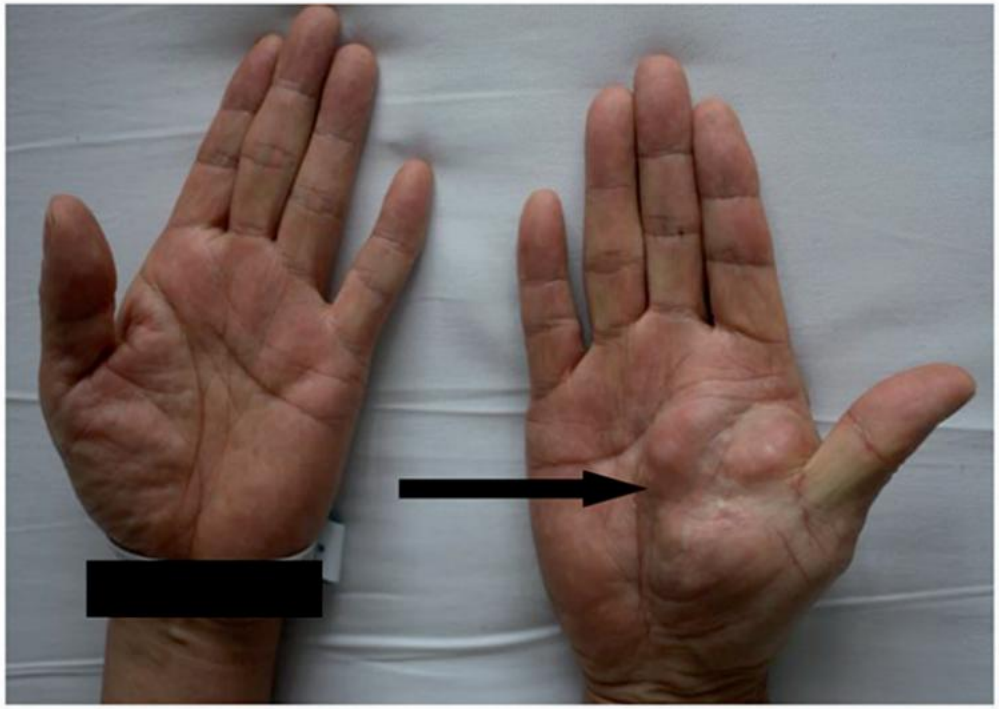


Figure 1. Irregular lump located in the thenar eminence of the right palm

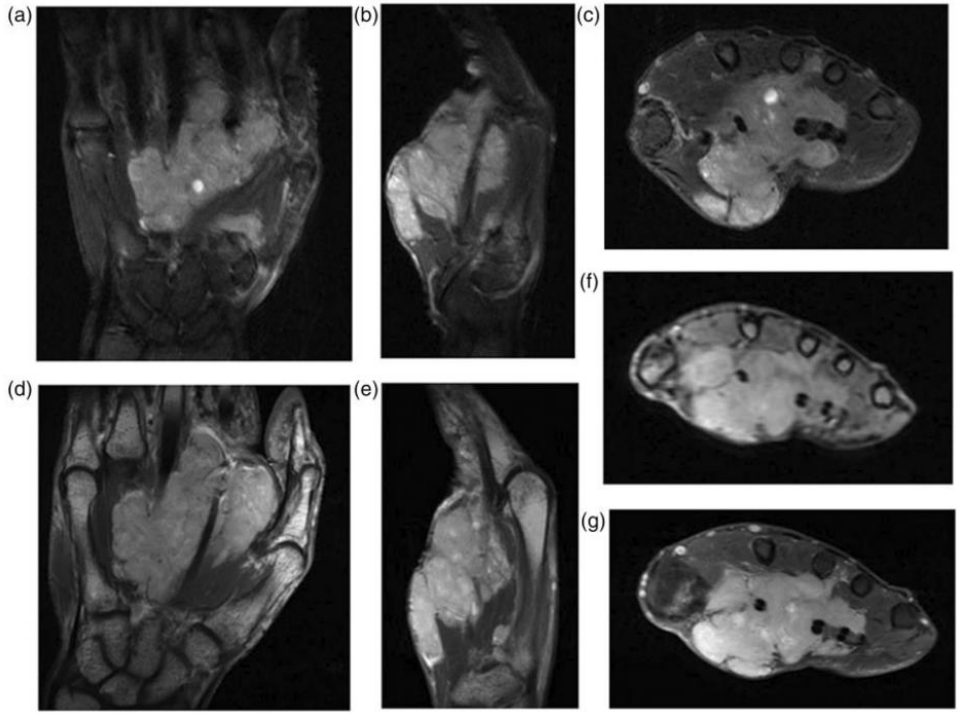


Figure 3. Magnetic resonance imaging revealed an irregular mass. The tumor was generously enhanced by gadolinium. (a, d) Coronal position. (b, e) Sagittal position. (c, f, g) Horizontal position. (a–c) T2-weighted images with fat suppression technique. (d–f) T1-weighted images enhanced by gadolinium. (g) T1-weighted images enhanced by gadolinium with fat suppression technique

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Bone Disease Markers

Disease	Calcium	Phosphorus	PTH	Vitamin D	Alkaline Phosphatase	Biomarker
Osteoporosis	Normal	Normal	Normal	Low	Normal/high	Cathepsin K C-telopeptide
Rickets Osteomalacia	Low	Low	**High**	Low	High	Osteocalcin
Paget's disease	Normal	Normal	Normal	Low	**High**	Osteopontin RANKL
Hypophosphatasia	Normal/high	Normal/high	Normal/low	Normal	**Low**	High Vitamin B6 PEA levels
X-linked Hypophosphatemia	**High**	Low	Normal	Normal/low	High	PHEX gene FGF23
Tumor-induced Osteomalacia	Normal	Low	Normal	**Low**	High	FGF23

Werner de Castro G R, Buss Z, Rosa J, et al. (May 31, 2019) Evaluation of Bone Metabolism Biomarkers in Paget's Disease of Bone. Cureus 11(5): e4791. DOI 10.7759/cureus.4791

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