Interhospital Endocrine Conference

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Mahidol University
Faculty of Medicine Ramathibodi Hospital

# A 58-year-old man progressive left thigh pain

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# Atypical Femoral Fracture & Tumor-Induced Osteomalacia

# Learning Point
# #1 Diagnosis AFF?

# Atypical Femoral Fracture

Fracture must be located along the **femoral diaphysis**
from just distal to the lesser trochanter to just proximal to the supracondylar flare

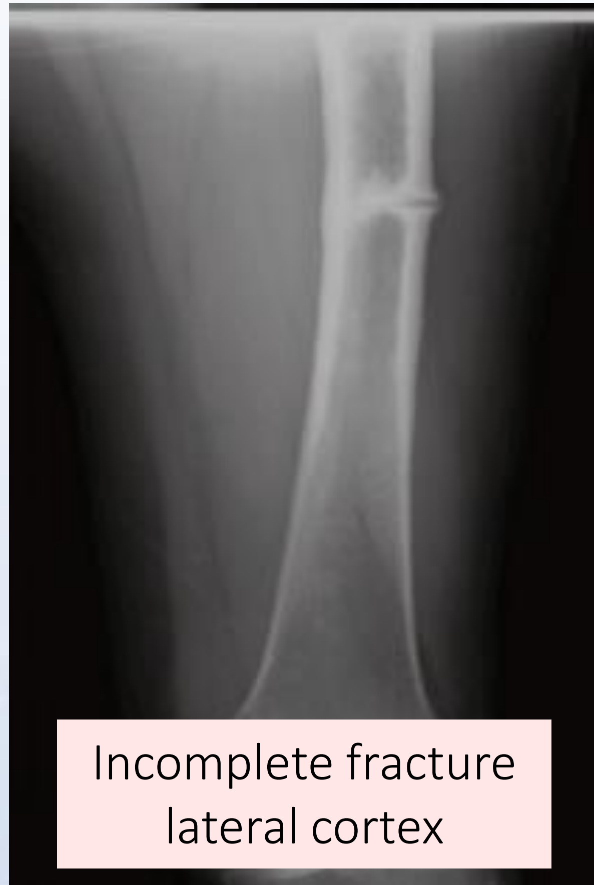
## Major features (4 of 5)

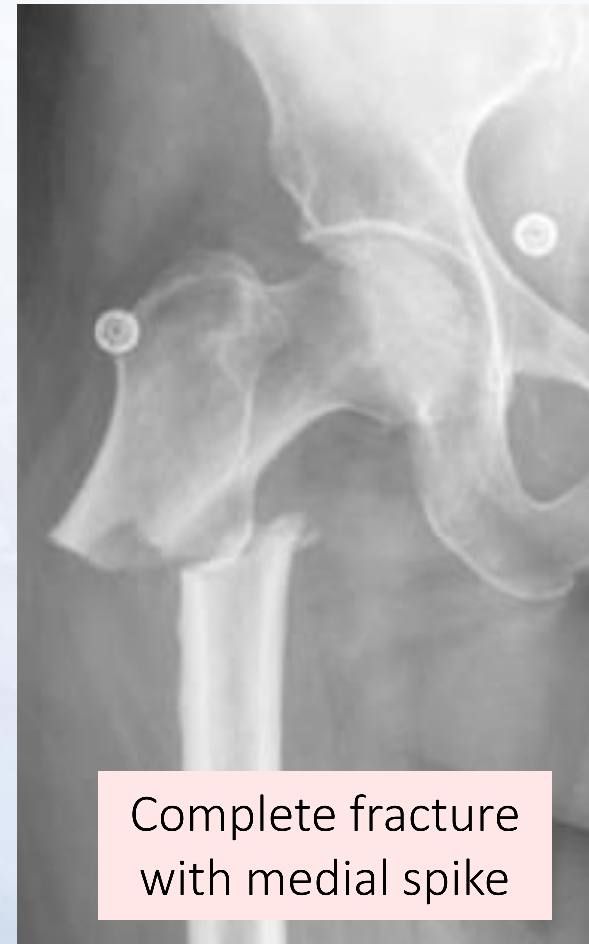
1. Associated with **minimal or no trauma**, as in a fall from a standing height or less
2. **Fracture** line originates at the lateral cortex and is substantially **transverse** in its orientation, although it may become oblique as it progresses medially
3. **Complete fractures** extend through both cortices and may be associated with **a medial spike or incomplete fractures involve only the lateral cortex**
4. **Noncomminuted** or minimally comminuted
5. Localized periosteal/endosteal thickening of the lateral cortex at the fracture site (“beaking”or“flaring”)

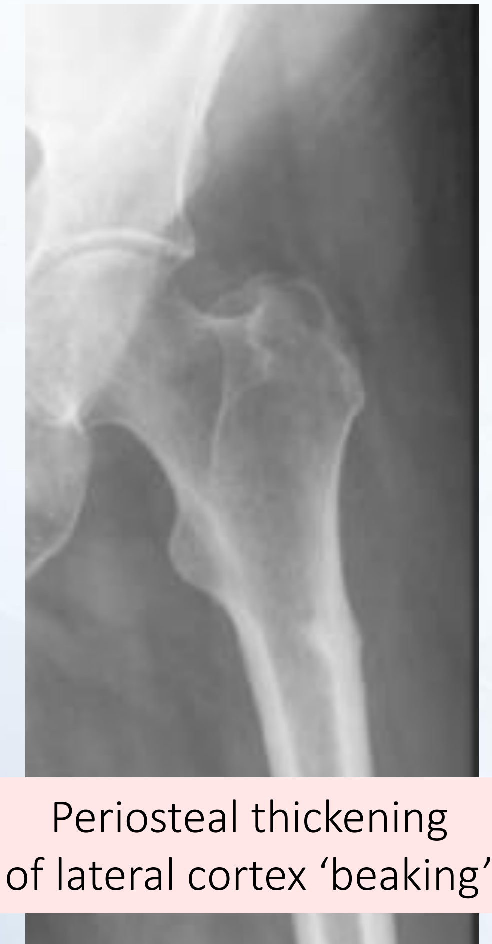
Excludes, periprosthetic fractures, pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget’s disease, fibrous dysplasia)

Shane E, et al. *J Bone Miner Res*. 2014 Jan;29(1):1-23.

# Atypical Femoral Fracture




*EFORT Open Rev.* 2018.
Black DM, et al. *Endocr Rev.* 2019.

# Atypical Femoral Fracture

↑Daily loading
Younger age and/or > physical activity
Bone geometry
Bone microarchitecture
↓Bone tissue properties
↓Microdamage repair
Coupled bone formation
Glucocorticoids
Targeted bone resorption
BP
+ Denosumab
↑↑Strain magnitude and distribution
Femoral bowing
↑Microdamage
AFF
Other factors such as genetics or metabolic bone disease could influence several steps in this process

Black DM, et al. *Endocr Rev*. 2019.

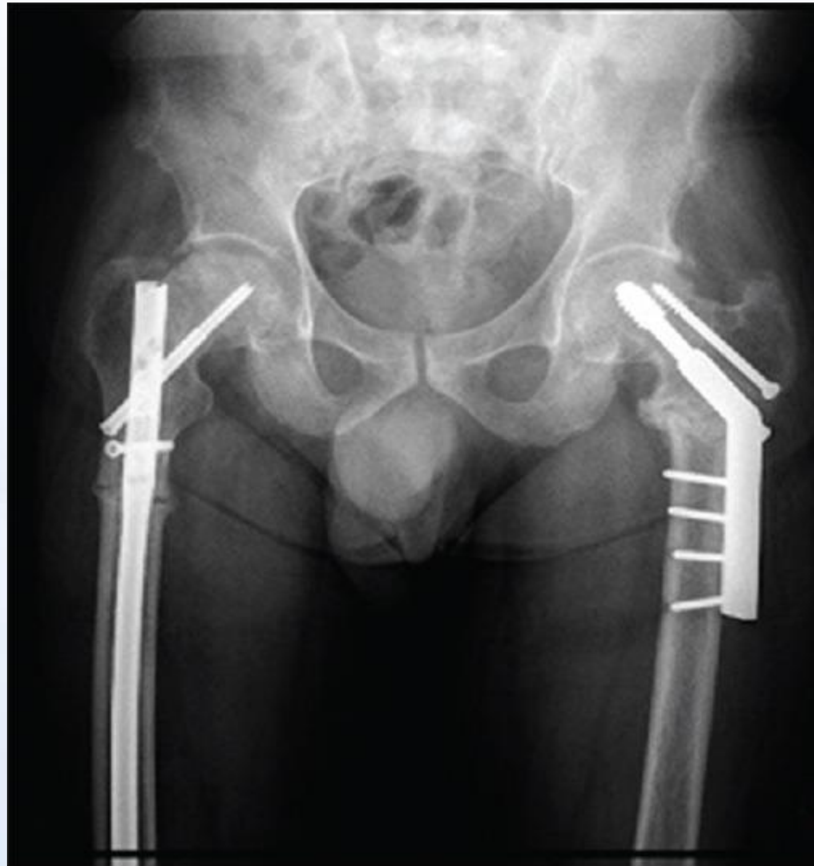
# Atypical Femoral Fracture

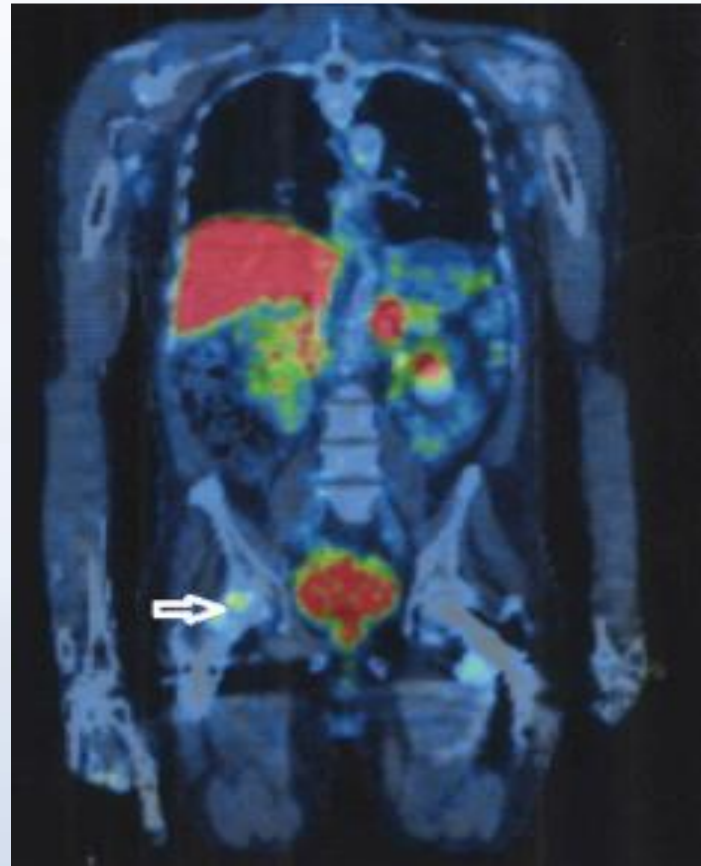
Risk factor (non anti-resorptive)

1. Genetic metabolic bone: Hypophosphatasia, X-linked hypophosphatemia, Osteopetrosis, Osteogenesis imperfecta
2. Impaired mineralization: **Osteomalacia,** Vitamin D deficiency
3. Medication: Glucocorticoid, PPI
4. Comorbidities: Rheumatoid arthritis
5. Femur geometry: Femoral bowing, Varus hip alignment

Georgiadis GF, et al. *J Orthop Case Rep*. 2021

# AFF from TIO: case report

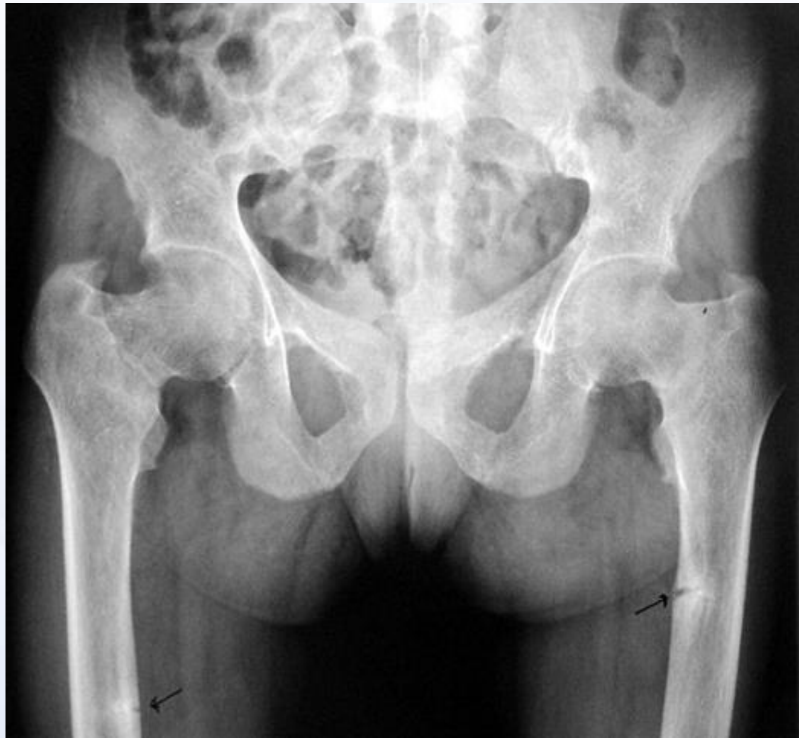


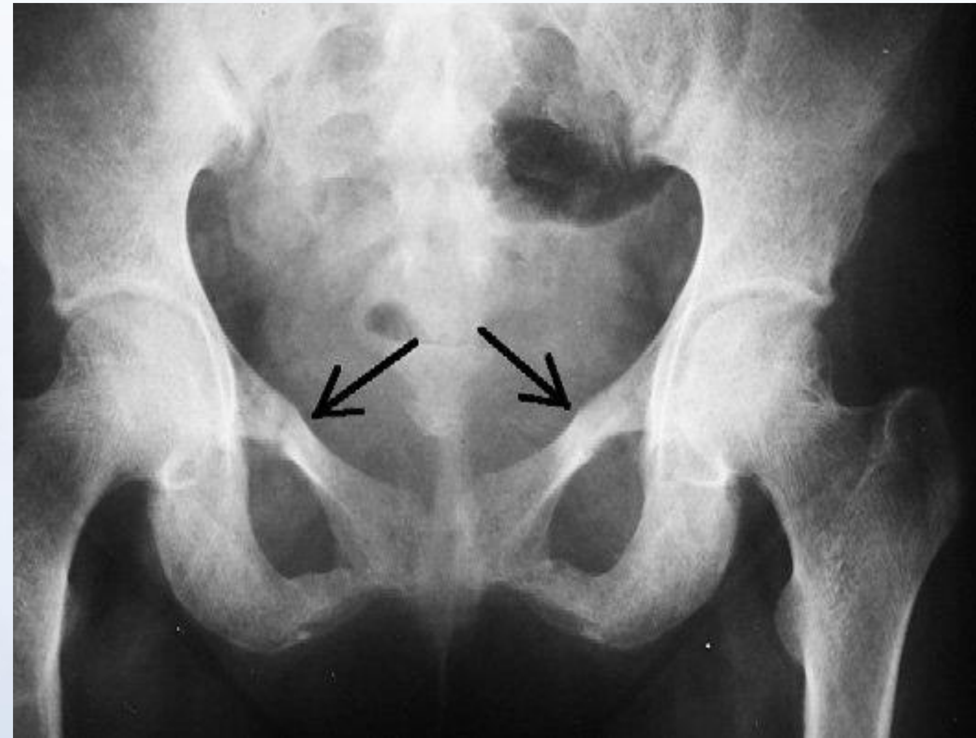


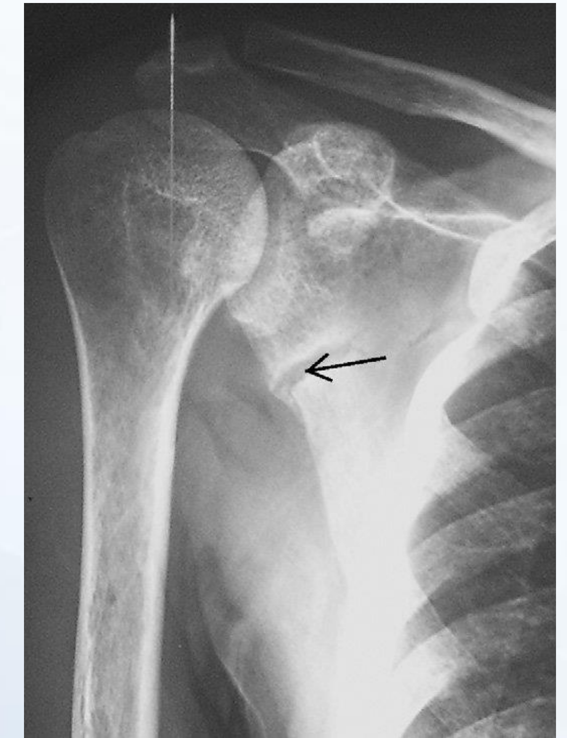
- 59-year-old man presented with a long-standing history of myalgia, bone pain, and fracture of the bilateral femur.
- A biochemical evaluation: hypophosphatemia secondary to phosphaturia.
- $^{68}$Ga DOTANOC PET/CT: tumor in the right femoral head
- After tumoral resection → clinical/biochemical parameters improvement

Shetty S, et al. A mysterious case of recurrent fracture: Tumour-induced osteomalacia. *J Family Med Prim Care*. 2022

# Looser's zone of Osteomalacia



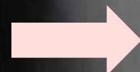




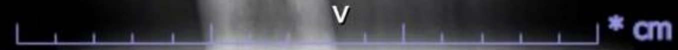
Common sites affected include proximal femurs medially, pubic rami, and scapula

Bhan et al. *Endocrinol Metab Clin North Am.* 2014

AFF finding



Looser's zone




# Rt Femur AP

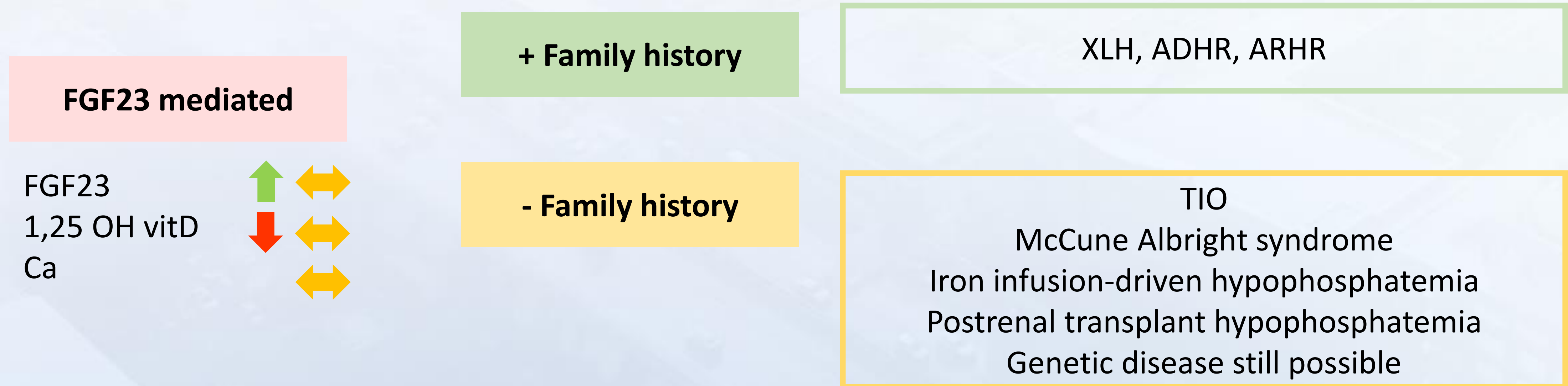
R

RAMADHIBO

# #2 DDx of Hypophosphatemic Rickets/Osteomalacia

# Hypophosphatemic Rickets/Osteomalacia

1. Chronic decrease intestinal absorption (normal to high TmP/GFR)
2. Renal phosphate wasting (low TmP/GFR)




XLH = X-link hypophosphatemic rickets
ADHR = Autosomal dominant hypophosphatemic rickets
ARHR = Autosomal recessive hypophosphatemic rickets

Ackah SA, Imel EA. Approach to Hypophosphatemic Rickets. *J Clin Endocrinol Metab*. 2022

# Hypophosphatemic Rickets/Osteomalacia

1. Chronic decrease intestinal absorption (normal to high TmP/GFR)

2. Renal phosphate wasting (low TmP/GFR)

**Non FGF23 mediated**

FGF23 ↓
1,25 OH vitD ↑ ↔
Ca ↑ ↔

| | |
|---|---|
| **Low urine calcium** | Primary hyperparathyroidism |
| **High urine Calcium without glucosuria amino aciduria** | Hereditary Hypophosphatemic Rickets with Hypercalciuria<br>Diuretics |
| **High urine Calcium with glucosuria amino aciduria** | Fanconi syndrome<br>(Drug: ARV – TDF, Anticancer, Heavy metals) |

Ackah SA, Imel EA. Approach to Hypophosphatemic Rickets. *J Clin Endocrinol Metab*. 2022

# #3 Tumor Localization

# TIO: Tumor Localization

Functional localization

**Anatomical localization**
Contrast-enhancing MRI, CT

Consider venous sampling FGF23
If uncertain Dx of single lesion or multiple lesions

*** But 37.5% of the tumor was not identified ***

Minisola S, et al. Endocr Rev. 2023.

# TIO: Tumor Localization

## Functional localization

Somatostatin receptor: mainly SSTR2 (not specific)

→ Radiolabeled SSTR analogs with SPECT/PET

**Octreotide: SPECT/CT**

- ❑ Indium-111 Octreotide - Octreoscan,
- ❑ Technetium-99m hydrazinonicotinamide (HYNIC)-Octreotide (sense 86.3%, spec 99.1%)

**Gallium-68 with SSA peptide: PET/CT**

- ❑ **DOTATATE (high affinity to SSTR2)** (sense 100%, spec 91%)

**Fluorine-18 fluorodeoxyglucose (FDG): PET/CT**

- ❑ lower performance/sensitivity (sense 67%) in identifying tumor

False positive: inflammatory tissues, in sites of fracture

Minisola S, et al. Endocr Rev. 2023.

# TIO: Tumor Localization

Lesion not identified

Treat

Medical therapy

Phosphate and 1,25-dihydroxyvitamin D/ vitamin D analogs or Burosumab

Conventional Medical Treatment

Lesion identified

Resectable

Treat

Surgical resection with wide margins

Not resectable

Treat

Ablation[a] or Medical therapy

Phosphate and 1,25-dihydroxyvitamin D/ vitamin D analogs or Burosumab

Dahir K, et al. J Endocr Soc. 2021

# Burosumab

**Benefit of treatment**

- Alleviate symptoms, Rapidly increase TmP/GFR
- Improved bone histomorphometric parameters
- Enhanced fracture/pseudofracture healing

**Dose of treatment**

- Initial 0.3 mg/kg (titrate - serum PO4 level) -> maximum dose 2 mg/kg SC weekly

June 2022, Burosumab is approved in the USA for the treatment of FGF23-related hypophosphatemia in TIO associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized (age 2 years or older)

Minisola S, et al. Endocr Rev. 2023.