Consensus on clinical management of tumor-induced osteomalacia

Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome caused by excessive production of fibroblast growth factor 23 (FGF23) by a tumor, which often arises from a mesenchymal origin.[1, 2] FGF23 plays a key role in the regulation of phosphate homeostasis. Its classic effects are inhibition of the expression of sodium-phosphate cotransporters 2a and 2c on proximal renal tubules, which results in reducing phosphate reabsorption and hypophosphatemia. In addition, FGF23 inhibits the production, increases the degradation of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D],[1, 2] and subsequently decreases intestinal phosphate absorption. Most clinical symptoms of TIO are the consequences of prolonged FGF23-mediated hypophosphatemia as muscle weakness, bone pain, impaired mobility, and fractures.[3, 4]

The first case of TIO was described in 1947 by McCance,[5] but it is not until 1959 that the relationship between tumors and osteomalacia was unveiled.[6] After that, a series of studies of TIO were conducted.[7–9] Due to their small sizes, slow-growing, unexpected locations, and unapparent focal symptoms by TIO tumors, the causative tumors are difficult to detect by conventional imaging modalities. After the applications of somatostatin receptor (SSTR) imaging,[10–13] a large number of TIO cases have been reported.

However, TIO is still a rare disease because about 500–1000 cases have been reported in the literature.[14, 15] TIO most commonly affects middle-aged adults,[3, 4, 16, 17] but cases have also been reported in children and the elderly.[18–22] Men and women are equally affected.[3, 4, 16, 17] The exact prevalence or incidence from a population-based study is absent. To date, there is only one nationwide epidemiological survey of FGF23-related hypophosphatemic diseases conducted in Japan, which included not only TIO but also other FGF23-related rickets. The numbers of patients with TIO and X-linked hypophosphatemic rickets (XLH) were similar indicating that there are about 50 new TIO patients in Japan annually.[23]

Clinical diagnosis and management of TIO are challenging. Given the rarity of this condition, many medical practitioners would overlook the clinical and biochemical manifestations, and perhaps therefore the initial misdiagnosis rate was 95.1%.[24] In addition, accurate localization and successful surgical removal of the responsible tumor are the definitive treatment. With the development of imaging and surgical techniques, more and more TIO patients recovered from hypophosphatemia and its related symptoms after tumor excision. However, a recent retrospective study revealed that nearly 20% of TIO persisted or recurred after primary surgery.[25] Under such circumstances, an evidence-based consensus and recommendation for the diagnosis and management of TIO are in urgent need. The scope of the present report is to review and update the assessment and treatment of TIO. Evidence-based recommendations are provided in this expert consensus.

Methods

The writing committee consists of experts representing endocrinology, pathology, radiology, nuclear medicine orthopedics, stomatology, and rhinology departments. Experts in the writing committee were invited to develop this consensus based on their publication record and the number of TIO patients they have participated in the diagnosis and treatment. From the evidence, especially high-quality evidence is limited or even nonexistent for this rare disease; we provide recommendations based on an expert's review on the limited data, as well as their experiences and opinions when data are unavailable. This process may be less systemic than the GRADE methodological framework; however, it is unrealistic to gather more reliable evidence without an international consensus to promote standard management of TIO.

A comprehensive literature search was conducted on PubMed before 16 August 2020. Publications in English were only considered. The search strategy was developed based on the Mesh terms and text word of "tumor-induced osteomalacia," "tumour-induced osteomalacia," "TIO," "Oncogenic osteomalacia," "OO," "OOM," "phosphaturic mesenchymal tumor," "phosphaturic mesenchymal tumor mixed connective tissue variant," "PMT," and "PMTMCT." Additional relevant articles on clinical manifestations, histopathological features, tumor localization, and treatments were also searched in PubMed when supplementary information was necessary. More than 600 articles were comprehensively reviewed and 197 of them were referenced here.

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Pathophysiology

As an important phosphatonin, FGF23 has been demonstrated to be overexpressed in tumors of TIO at both RNA and protein levels.[26] The action of FGF23 is mediated by binding to its receptor complex, fibroblast growth factor receptor 1 (FGFR1), and the co-receptor α-Klotho.[27] It downregulates sodium-phosphate cotransporters protein 2a and 2c, resulting in reduced phosphate reabsorption at the proximal renal tubules.[28, 29] In addition, it suppresses 1-alpha-hydroxylation and promotes 24-hydroxylation of 25-hydroxy vitamin D, and $1,25(OH)_2D$, leading to decreased $1,25(OH)_2D$ which reduces the phosphate absorption in the intestine.[28] Besides FGF23, expression of several matrix-associated proteins, such as secreted frizzled-related protein 4 (SFRP4), matrix extracellular phosphoglycoprotein (MEPE), and FGF7 was found to be elevated in tumors,[30, 31] which has been proved to promote phosphate wasting in animal experiment.[31–33] However, the elevation of these proteins has not been reported in the serum of TIO patients. Given the above, overproduced FGF23 from tumors leading to hypophosphatemia is regarded as the key factor in the pathogenesis of TIO.

Identification of fusion genes shed new sights into tumorigenesis of TIO. The first identified fusion gene was FN1 (encoding gene of fibronectin)–FGFR1 (encoding gene of FGFR1), which

was found in 42% (21/50) of tumors in the largest studied cohort to date.[34] The FN1–FGFR1 fusion gene preserves a large part of the extracellular domain of fibronectin, the ligand binding, and transmembrane and intracellular signaling domains of FGFR1.[35] Fibronectin, a highly expressed extracellular protein, probably provides its strong promotor to stimulate the overproduction of fusion gene, including the 3′ portion of FGFR1 which is a known oncogene in various malignant tumors.[36, 37] Fibronectin can also polymerize and bind to other extracellular matrix proteins, which may facilitate the auto-dimerization of the fusion protein and lead to ligand-independent activation of FGFR1 signaling.[34] The ligand-binding domain of FGFR1 is predicted to be preserved, which might imply a ligand-dependent manner (including FGF23). Overproduced FGF23 partially caused by activation of FGFR1 signaling further activates the fusion protein, potentially leading to an autocrine or paracrine feed-forward signaling. Interestingly, α-Klotho, the obligatory co-receptor for FGF23–FGFR1 binding, was found to be lowly expressed in fusion-positive tumors.[35] It might be explained by enhanced binding affinity of the fusion protein to FGF23 due to loss of the first Ig-like domain of FGFR1.[34, 35] However, recent studies revealed that overexpression of α-Klotho (or β-Klotho),[38] especially in fusion-negative tumors,[39] might result in an FGF23–FGFR1 autocrine loop that in turn drives the overexpression of FGF23 and tumorigenesis through activated FGFR1 signaling.

The second fusion gene FN1–FGF1 was demonstrated in 6% (3/50) of tumors.[34] The fusion protein retains nearly the entirety of FGF1 and might function like normal FGF1, which is a crucial ligand for all FGFRs.[40] The fusion protein also retains the auto-dimerization domain of fibronectin to dimerize and was speculated to bind the membranous FGFR1 in a 2:2 ternary fashion to activate FGFR1 signaling.[34]

Hypoxia-inducible factor-1α (HIF-1α) is another new finding, which was shown to be overexpressed and co-localized with FGF23 in tumors resected from two TIO patients.[41] HIF-1α inhibitors decreased HIF-1α and FGF23 protein as well as HIF-1α-induced luciferase reporter activity *in vitro*. These results suggest that HIF-1α is a transcriptional activator of FGF23 and upregulated HIF-1α might partially explain the overproduced FGF23 in TIO.

Diagnosis

General approach

The diagnosis of TIO is based on the association of clinical manifestations, biochemical findings, and the identification of the tumor (most importantly). Patients with clinical and/or radiological signs of rickets/osteomalacia, especially those with chronic hypophosphatemia, should be suspected.[3, 4, 42] Besides, other causes of hypophosphatemic rickets/osteomalacia should be excluded at the very beginning of the diagnosis.[15]

Clinical features

Clinical manifestations can vary widely in patients, but some typical symptoms generally occurred in the vast majority of patients with TIO. These typical symptoms are actually similar to those described in the first case of TIO,[5] which including pain and muscle

weakness.[3,4,16,24,25,43–47] In children with TIO, decreased growth velocity can also be found.[18] The pain is usually described as a widespread bone pain developed from weight-bearing sites, such as feet or lower limbs, and gradually progressed upward to bones of the whole body except the head. Muscle weakness, generally proximal muscle weakness, occurs in almost 100% of reported cases but it is not specific enough to make a diagnosis. Impaired mobility, or described as gait abnormality or trouble walking in different studies, is a result of bone pain and muscle weakness. With the progression of untreated disease, the severity of impaired mobility aggravates, resulting in the loss of self-care ability, and being bedridden. Other common symptoms have been summarized in retrospective studies with at least five cases including height loss, fractures, and bone deformities.[4, 16, 24, 44–47] The prevalence of fractures is 40–100% according to previous studies.[4, 16, 24, 42, 43, 45–47] Fractures mainly happen in ribs, vertebral bodies, pelvis, and femurs; and the sites of fractures are not related to the sites of causative tumors. Of note is that these fractures were often described as pathological fractures in previous studies, while the risk of traumatic fracture may also increase in these patients since their impaired mobilities.

Symptoms related to tumor masses themselves are observed in tumors located in oral, nasal, or aural regions occasionally. These symptoms can be obstructive symptoms, such as breathing or swallowing difficulties, epistaxis, deafness, facial nerve palsy, or just a palpable mass by the tongue,,[48–50] and therefore should be covered in the questioning. Tumors of the jawbone are usually solitary mass involving mandibular and/or maxillary gingiva. Tumors originated from the gingiva show localized thickening and swelling of the gingiva, or a mass like an epulis.[51] The affected teeth often become loose and eventually fall off because of the soft alveolar bone. Occasionally the lesions would extend to the inferior alveolar nerve canal, however, generally there is a little symptom, such as numbness of the lower lip. Metastatic disease is even rarer[52–61] and the lungs seem to be a vulnerable organ.[43, 55–58, 62]

The problems of psychiatric symptoms are largely invisible. However, these symptoms do exist[63] and may evolve into a suicide attempt in severe cases.[64] The psychiatric symptoms in TIO patients may provoke by pain or decreased social capability.

Physical examinations (PEs) can find signs associated with typical symptoms. Typically, the patients present gait abnormalities, pressing pain of a wide range of bones, and decreased distance between costal margin crista iliaca, which indicate the compression of lumbar vertebral bodies. In severe patients with bone deformities, barrel chest, kyphosis, and varus/valgus deformities of lower limbs may emerge. Besides, PEs can discover local lumps that responsible for the disease in some cases. In a retrospective study, local lumps that turned out to be causative tumors were found in 14.6% of patients.[24] Thus, any local lumps, especially those are new-found in recent years, should not be neglected.

Most cases of TIO develop in an adult with an average age of diagnosis of 40–45 years,[3,4,16,17,25,44] while there are also case reports of underage patients,[18–22] and the youngest patient was diagnosis at 2-year-old.[65] Patients with TIO always coexist with responsible

tumors for years and even decades. It is hard to answer how long it takes from TIO tumorigenesis to occurrence of related symptoms, and the duration from the onset of symptoms to correct diagnosis may range from 1 year to as long as >20 years.[25] During this period, these tumors do not cause death but devastate patients' independence and quality of life progressively until effective intervention.

Biochemical characteristics

Biochemical findings play an important role in the diagnosis of TIO. Except for the high level of FGF23 secreted by the tumor, the main biochemical characteristics of TIO are low serum phosphate due to the reduction of tubular maximum reabsorption of phosphate (TmP)/glomerular filtration rate (GFR), increased serum alkaline phosphatase (ALP), and inappropriately normal or reduced concentration of $1,25(OH)_2D$.

Serum phosphate

The normal reference range of serum phosphate for an adult is 0.81–1.45 mmol/L. It is worth noting that serum phosphate levels vary according to age in childhood, which needs to be carefully considered when assessing whether hypophosphatemia is present or not.[66] Serum phosphate in TIO patients is far below the normal range in a retrospective analysis,[67] serum phosphate level was 0.48 ± 0.13 mmol/L, with a range of 0.17–0.80 mmol/L.

Serum alkaline phosphatase

Serum ALP, especially bone alkaline phosphatase (BAP) concentrations are increased in TIO patients.[4, 46] They are important biochemical markers to differentiate osteomalacia from hypophosphatasia, which is also characterized by impaired mineralization but with low ALP and BAP levels on the contrary.

TmP/GFR

In healthy people, when the serum phosphate level falls <0.65 mmol/L, urine phosphate decreases to trace or undetectable.[68] However, in TIO patients, the situation is different because of the decrease in TmP. The evaluation of renal tubular reabsorption of phosphate (TRP), which is estimated by calculating TmP, is crucial for the diagnosis of renal phosphate wasting. Patients suspected of TIO should under a drug-eluting for at least 1 day from phosphate supplementation and fast overnight. Phosphate and creatinine levels in the urine were collected over 2 h from the patient and in the blood sampled at the midpoint of the urine collection. TmP/GFR minimizes variation, which is due to differences in lean body mass. The percentage of TRP is calculated using the following equation: $100 \times (1 - \text{urine phosphate} \times \text{serum creatinine}/\text{serum phosphate} \times \text{urine creatinine})$ with a normal range of 85–95%. TmP/GFR is read on the Walton-Bijvoet chart [Supplementary Figure 1] by drawing a line of serum phosphate (left coordinate axis) and TRP to the right coordinate axis (normal range: 0.80–1.35 mmol/L).[69]

Serum FGF23

The levels of FGF23 are a unique and essential indicator for the diagnosis and surveillance of TIO. Both intact molecule formats (iFGF23) and carboxy-terminal fragments of the molecule

(cFGF23) are available.[70] Elevated levels of serum iFGF23 or cFGF23 could be observed in the majority of TIO patients, while the iFGF23 levels ranged from 44.1 pg/mL to 14922.3 pg/mL are reported. A high circulating level of FGF23 is an indicator of malignant tumors and a predictor of the surgery outcome.[25] It should be noted that completely normal FGF23 levels reveal successful surgery and clearance of the lesion. On the contrary, failure of normalization is sensitive in prompting residual lesion or rare multifocality.[71, 72] During the follow-up, if the high level of FGF23 persists or recurs, it warns that an incomplete resection or a relapse exists.

Serum 1,25(OH)$_2$D and 25-hydroxyvitamin D

Since excessive FGF23 suppresses renal 1,25(OH)$_2$D production by downregulating renal 1α-hydroxylase gene expression as well as upregulating 24-hydroxylase gene expression.[73] Reducing or inappropriately normal concentration of 1,25(OH)$_2$D is observed in TIO patients.

Although 25-hydroxyvitamin D deficiency can be seen in TIO patients, it is not due to the tumor itself.[24, 45] If the patient shows high FGF23, even with the presence of vitamin D deficiency, FGF23-related hypophosphatemia can be diagnosed.[74]

Serum parathyroid hormone (PTH)

Serum PTH levels can be normal or elevated.[75] Elevation of PTH levels reflects secondary hyperparathyroidism caused by low levels of 1,25(OH)$_2$D and worsens renal phosphate wasting. Prolonged secondary hyperparathyroidism in TIO can lead to tertiary hyperparathyroidism,[76] especially those who have received phosphate supplementation with inadequate activated vitamin D for a prolonged period.[77]

Imaging

Bone features on radiography

TIO adult patients demonstrated features of osteomalacia with obscur bone structure, concave changes of vertebrae, inward bending of the pelvic sidewall, as well as pseudofracture (Looser zone) on the radiography. TIO child patients presented features of rickets with frayed or cupping metaphysis. Since most tumors of TIO are eccentric and located in the epiphysis,[78] any such lesion in the long bones with osteomalacia on radiography should raise a suspicion of the tumor.

Dual-energy X-ray absorptiometry (DXA)

DXA measurements can be helpful to understand the low bone mineral status and predict fracture risk for TIO patients who are prone to fractures.[79] As known that surgical complete tumor resection may lead to resolution of symptoms as well as the improvement of bone mineral density.[80, 81] Increasing in bone density may be faster in spine and hip compared with radius in TIO patients after tumor resection.[80, 82]

Tumor localization

Tumor localization is the most challenging and important part of the diagnosis process of TIO. A stepwise approach to locating the causative tumor is widely recommended since tumors are usually small and slow-growing with unexpected locations over the whole body [Supplementary

Figure 2].

Physical examination

The first step is to screen the whole body for suspected lesions. This step comprises a thorough inquiry and PE. It is important to emphasize the value of general PE. Careful questioning of the patient asking whether any “lumps and bumps” has been felt and then on PE carefully and completely feeling for tumors in areas such as the soles of the feet and the popliteal area can be very revealing.[48, 49]

Functional imaging

Functional imaging approaches,[83–100] including SSTR imaging, ^{18}F-FDG PET/CT, and bone scan, have played a significant role in the detection of suspicious lesions of TIO.[87–89, 92, 93, 100–109] SSTR imaging methods comprise octreoscan with SPECT/CT and ^{68}Ga-DOTA-conjugated-somatostatin-receptor-targeting-peptides (^{68}Ga-DOTA-SST) PET/CT scan. The culprit tumors of TIO are reported to overexpress SSTR, mainly subtype 2, allowing the use of SSTR imaging.[110] Either SSTR imaging method is always recommended as a first-line imaging investigation, depending on their comparatively high sensitivity and accuracy in TIO lesion localization.[101, 103] Due to higher SSTR2 affinity of ^{68}Ga-DOTA-SST than that of ^{99m}Tc-HYNIC-TOC, it is always used for re-screening the lesions, which were negative in octreoscan.[111] When SSTR imaging methods are unavailable, ^{18}F-FDG PET/CT shall be obliged to be second-line for tumor location, while the sensitivities of ^{68}Ga-DOTA-SST, ^{99m}Tc-HYNIC-TOC, and ^{18}F-FDG PET/CT were reported as 87.6–90%, 83%, and 67%, respectively.[101, 112] The sensitivity of bone scan (20–30%) is the lowest one among three functional imaging approaches. Therefore, it is always employed for osteomalacia evaluation instead of lesion localization, especially for those with bone pain.[100]

The fractures always demonstrate a high accumulation of tracers on SSTR imaging because inflammatory cells express SSTR2.[113] Even though SSTR imaging can differentiate the fractures’ avidity from the TIO lesion properly, additional X-ray or CT is still recommended to confirm the fractures.

Anatomical imaging

Once the TIO tumors are suspected by function imaging or PEs, the next step is to confirm the lesions by anatomical imagings. Based on different sites of suspected masses, techniques including MRI, CT, radiography, or ultrasound may be used. When accessible, MRI and CT are recommended because of their advantage in high resolution.

MRI

MRI skeletal screening has been frequently used to detect TIO tumors since it has inherently superior soft-tissue resolution with better imaging characteristics for the tumors in either soft tissues or bones.[114, 115] Since MR imaging characteristically can delineate tumors in detail and identify accurately extension to critical structures around the tumor, it is extremely useful for surgery planning to prevent local recurrence and injury to the critical structures around the tumor.

Among the different sequences for image acquisition, short-tau inversion recovery (STIR) images and T2-weighted fat-suppressed MR images[116] can clearly show tumor areas with high signal intensity,[114] which should be used preferentially for tumor locations.[117] Contrast-enhanced MRI has proven to be extremely helpful for differential diagnosis, particularly for intracranial tumors.[118, 119] Although whole-body MRI can be used for detecting multifocal tumors throughout the body, it has the limitation for much longer time-consuming for screening compared with other whole-body modalities (such as PET/CT). In addition, whole-body MRI is usually neither sensitive nor specific for tumor detection.[120]

CT

CT has the advantage to delineate bone structure and tumors, particularly at irregular bone sites. Head CT can detect tumors in paranasal sinuses. For tumors located in the jawbone, the panoramic image and cone-beam CT could help to determine the extent of bone destruction caused by lesions. Chest high-resolution CT could demonstrate lung metastasis from malignant TIO tumors.[8, 121–123]

Venous sampling

Venous sampling with measurement of FGF23 is also used in several cases.[124–132] One study utilized systemic venous sampling, which collected 16–22 blood samples from each patient, to locate causative tumors and succeed 8 of 10 consecutive patients with suspected TIO.[128] Another study underwent selective venous sampling in 14 cases and proposed an FGF23 diagnostic ratio of 1:6 (maximum FGF23 value/mean FGF23 value) to diagnose causative tumors, with a sensitivity of 0.87 and a specificity of 0.71.[129] Of note, selective venous sampling is particularly useful to confirm causative tumors in patients with multiple suspicious regions, or patients with relatively high surgical risk or trauma.

Pathology

TIO-associated tumors are generally of mesenchymal origin.[7, 8, 133] These mesenchymal tumors are histologically polymorphous and have been diagnosed as giant cell tumors, hemangiopericytomas (HPCs), non-ossifying fibromas, fibrosarcomas, osteosarcomas, osteoblastomas, chondroblastomas, chondrosarcomas, sclerosing hemangiomas, angiofibromas, angiolipomas, or other mesenchymal tumors.[8, 9, 62] In 1987, Weidner and Santa Cruz coined the term “phosphaturic mesenchymal tumor” (PMT) and categorized these mesenchymal tumors into four morphological subtypes: (1) PMT, mixed connective tissue type (PMTMCT); (2) PMT, osteoblastoma-like; (3) PMT, nonossifying fibroma-like; and (4) PMT, ossifying fibroma-like.[8] With improved recognition of the histological spectrum, another landmark study by Folpe *et al*[9] in 2004 analyzed 32 cases of TIO-associated mesenchymal tumors with a comprehensive review of 106 cases in the literature and concluded that most tumors, both in their series and in the literature, were a single entity (PMTMCT) with a wide histological spectrum.

Most PMT present as non-specific soft tissue or bone masses and may contain calcified or hemorrhagic areas.[133] PMT of soft tissue at least focally infiltrate into surrounding tissues,

probably accounting for their high local recurrence rate. The neoplastic cells typically have a low nuclear grade with absent or minimal nuclear pleomorphism, absent to rare mitotic figures, and low Ki-67 proliferative index (<5%). The tumor contains a small, arborizing network of capillaries. Prominent hyalinized and branching HPC-like vasculature may also be found. The tumor typically produces a characteristic “smudgy” matrix that calcifies in a peculiar “grungy” or flocculent fashion, and sometimes osteoid, chondroid, and/or myxoid matrix. A variable component of osteoclast-like giant cells and mature adipose tissue are also common findings in PMT. PMT in the sinonasal and craniofacial bone may show some unique histopathological features.[9, 133, 134] PMT arising from alveolar bone is characterized by haphazardly and diffusely distributed small, irregular odontogenic epithelial nests.[51]

Although the histological criteria for malignant PMT have not been well developed, frankly sarcomatous features (high cellularity, marked nuclear atypia, elevated mitotic activity and Ki-67 proliferative index, and necrosis) support the diagnosis of malignant PMT. Malignant PMT typically appears as a recurrent or metastatic tumor.[51, 135]

By immunohistochemistry, FGF23, SSTR2A, NSE, CD99, CD56, Bcl-2, D2-40, CD56, CD68, SATB2, and ERG have also been demonstrated to be frequently expressed in PMT. Other mesenchymal markers including FLI-1, SMA, and CD34 were also expressed to varying degrees.[51, 136, 137] Although immunohistochemistry is considered to be non-specific and thus of limited value, the polyimmunophenotypic profile may favor the diagnosis of PMT. Although previous studies have used immunohistochemistry for detecting FGF23 expression, some pathologists believe that commercially available antibodies to FGF23 have questionable specificity and are not widely available, and prefer chromogenic *in situ* hybridization (CISH) for FGF23 expression detection in PMT. However, CISH is not commonly used in routine pathology practice. Besides, detecting the characteristic FN1/FGFR1 or FN1–FGF1 gene fusions by fluorescence *in situ* hybridization (FISH) or next-generation sequencing (NGS) can be of great value in the diagnosis of morphologically ambiguous cases, cases without a given history of TIO or so-called “Non-phosphaturic PMT” (tumors showing morphological features of PMT without TIO).

Limited data have been obtained regarding TIO-associated tumors other than PMT. The histopathological, immunohistochemical, and molecular features of these tumors remain unclarified. Due to the apparent difference in the clinical implications, great caution is recommended when diagnosing any other specific type of mesenchymal tumor as the cause of TIO. Rare TIO cases have been reported in patients with carcinomas including pulmonary small cell carcinoma and anaplastic thyroid carcinoma. The expression of FGF23 in tumor cells was confirmed in at least some of these cases.[133, 138, 139]

Differential diagnosis

The clinical manifestations of TIO are latent and non-specific. In lack of knowledge about TIO, missed diagnoses or even misdiagnoses with subsequent diagnostic and therapeutic delay are

commonly seen in reported TIO cases, accompanied by prolonged morbidity and poor prognosis.[43, 140–143] In a Chinese study, 95.1% of patients were initially misdiagnosed as an intervertebral disc herniation, spondyloarthritis, osteoporosis, and other diseases.[24]

Serum phosphate level is the key point for differential diagnosis. TIO patients had moderate to severe hypophosphatemia together with normal serum calcium, elevated serum ALP, and normal or slightly elevated PTH level. The diagnosis should be considered when patients are characterized as hypophosphatemic osteomalacia/rickets. It needs to be differentiated from other disorders of phosphate metabolism. Serum FGF23 levels, which should be low in the setting of hypophosphatemia, are elevated or inappropriately normal in TIO. It could be used to differentiate from non-FGF23-related hypophosphatemic disorders, such as hereditary hypophosphatemic rickets with hypercalciuria (HHRH) and antiretroviral medication-induced Fanconi syndrome.[15,120,144] FGF23-related hypophosphatemic rickets/osteomalacia are shown in Supplementary Table 1 including inherited diseases, such as XLH, autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR), and disease syndromes such as McCune-Albright syndrome, neurofibromatosis 1, and so on.[15, 120, 144] TIO is the acquired form of FGF23-related hypophosphatemic osteomalacia. In children and adolescents without a family history, as well as in patients whose tumors cannot be located, genetic testing should be considered for excluding inherited diseases.[15]

Management and Treatment

Surgery

Surgical treatment has been widely regarded as the gold standard of TIO treatment.[78, 145, 146] From the surgical perspective, the optimal treatment for TIO involves the complete removal of the disease-causing tumor.[78, 145, 146] In most cases, this procedure can correct biochemical abnormalities and accelerate the process of bone remineralization. However, even a small amount of tumor tissue remains, the patient's symptoms continue to present or relapse easily.[78, 147]

Orthopedic surgery

The specific plan of surgical treatment should be determined based on the anatomical location of the disease-causing tumor and the surgeon's clinical experience. It is worth noting that osteomalacia reduces bone quality and increases the risk of fractures, nonunion, and delayed healing.[79, 148, 149]

For tumors located in the bones, orthopedic surgical protocols reported in the literature mostly include tumor resection, tumor curettage, and intraosseous injection of bone cement.[78, 145] For tumors that are partly hidden and difficult to remove, tumor curettage or intraosseous injection of bone cement is advised.[78, 146, 150] After the curettage of the tumor, the tumor cavity should be treated sequentially with phenol, high-temperature electrocoagulation, and warm distilled water before allogeneic bone transplantation is performed.[78] Three-dimensional technology guided tumor resection is expected to be more accurate in intraoperative localization and helpful to complete tumor resection.[151] If residual defects are present after segment resection, artificial joint

prosthesis or allogeneic bone segments are used to reconstruct and stabilize the anatomical structure. Intraosseous injection of bone cement has also been tried in the treatment of TIO, but the efficacy of this procedure and its long-term outcomes need to be confirmed.[146, 150] Due to the complexity of the anatomical structure of the spine, it is usually difficult to completely remove the TIO tumor in the spine, bone cement filling may also be an adequate treatment option.[150] However, extreme caution should be paid against cement leakage into the spinal canal even subsequent compression of the spinal cord.

For tumors located in soft tissue, special attention should be paid to the identification and protection of local nerves, blood vessels, muscles, fascia, ligaments, and other important anatomical structures to ensure complete tumor resection and avoid secondary damage.

Nasal surgery

A recent study of 222 PMT patients revealed 29 (13%) cases located in the sinonasal area.[51] The operative principle is to remove the soft tissue tumor and the adjacent bone lesions completely. Because of the abundant blood supply, endoscopic resection of the tumor is often challenging.[152, 153] Here are the recommended endoscopic surgical steps, first open the normal sinus and determine the boundary of the tumor, then remove the soft tissue tumor along with the bone interface, and finally resect the involved bone. The intraoperative navigation system could also increase the safety and efficiency of endoscopic sinus and skull base surgery.[154, 155] In addition, highly vascularized tumors, which could cause massive intraoperative hemorrhage, can be managed by preoperative transcatheter arterial embolization or feeding artery ligation.[152]

For patients with nasal septum involved and extension to the contralateral sinonasal cavity, a bilateral surgical approach is suggested to remove the tumor completely.[152] However, the external technique through the osteoplastic flap or lateral rhinotomy or combined approach is needed when the tumor is too large or the site of the tumor is not suitable for an entirely endoscopic technique.[156, 157] For cases involving frontal sinus, tumors with lateral extension or involvement of neurovascular structures are an indication for an open approach.[156] The skull base, especially the cribriform plate and roof, is often involved. To resect the tumor completely, the bone of the skull base should be removed. The dural mater and intracranial lesions should also be resected if there are the dural and intracranial invasions. To avoid postoperative cerebrospinal fluid leakage, autologous flaps (free or vascularized locoregional flaps), and nonautologous grafts are suggested to be used to repair the skull base defect endoscopically.[158, 159] For tumors located in the temporal bone and lateral skull base,[152, 160, 161] The temporal skull base and intracranial invasion should be removed through the temporal craniotomy to achieve clinical remission. If the adjacent vital structures were invaded, incomplete resection of the tumor combined with local radiotherapy is necessary for the remission of symptoms.[153]

Oral surgery

All primary PMT in the jaw could be resected by surgery. The intraoral approach is mainly used as most primary lesions are located around the alveolar process. For the cases involving the

lower edge of the mandible and the mandible body, the submandibular extraoral approach could be used. Local massive osteotomy should be performed at 0.5 cm away from the tumor. As the lesions often involve a wider range in the cancellous bone, the bone wall should be further scratched after osteotomy until the bone hardness is normal. The teeth affected by the lesion should be extracted or removed together with the osteotomy.[162] If the lesion involves the inferior alveolar nerve canal, the lesion should be completely removed by curettage. The inferior alveolar neurovascular bundle in the nerve canal should be preserved as far as possible.[163] If the lesion involves the whole mandible body, the complete removal of the lesion may lead to the weakness or fracture of the left wall of the mandible, and the titanium plate should be used for fixation and reinforcement of the bone.

Generally, the primary oral lesion of PMT in the maxilla and mandible is easy to be removed completely. The causes of incomplete primary removal include: (1) Blurred boundary of primary PMT; (2) Difficult to identify the adjacent teeth affected by primary PMT or not; and (3) Important anatomical structures such as inferior alveolar nerve canal affected by primary PMT. If the tumor is not completely removed or the primary tumor recurs, more strict surgical standards should be adopted for complete removal. A few tumors would evolve into malignant tumors after multiple local recurrences.[55, 164] At this time, the principle of tumor-free radical surgery should be adopted.[152]

Postoperative recovery

Once the TIO-causing tumor is successfully eliminated, the circulating level of FGF23 drops rapidly in hours, phosphate concentration gradually increases, and typically returns to normal levels within 5 days (2–16).[4] The patient's symptoms begin to gradually improve within a few days or weeks,[4, 24, 45] but the completion of the process may take several months.[17] However, studies have shown that even with extensive tumor resection, the possibility of metastasis or recurrence persists.[147] Therefore, TIO patients require long-term follow-up.

Nonremission and recurrence

As mentioned above, serum FGF23 normalizes in hours after surgery and serum phosphate normalizes in days. Nonremission refers to a persistent disease without normalization or just a transient normalization in one or two tests of serum FGF23 and phosphate after surgery, while recurrence refers to a recrudescent condition after a sustained disease-free period of at least 1 month. We believe both nonremission and recurrence are conditions of refractory cases. Although TIO is curable by complete excision of the responsible tumor, refractory cases have been reported with a combined incidence of 0–57% in case series studies.[4, 9, 16, 43, 47, 62, 106, 136, 165–170] In most cases, the persist or recurrent tumors localize at the same sites of primary tumors, indicating the initial resections may be inadequate in these cases, even when surgeries have been performed according to the recommended protocol to excise all visible tumor with wide margins.[145] In a most recent study, the characteristics of refractory cases were reviewed in a total of 230 patients with TIO.[25] Among these patients, 24 patients had persistent diseases and 18 relapsed after initial

surgeries, suggesting a nonremission rate of 10.4%, a recurrent rate of 7.8%, and a combined refractory rate of 18.2%.[25] Refractory tumors showed several features that differ from the other tumors. Tumors located at the head and neck region showed the lowest refractory rate of 7.5%, whereas tumors located at the spine showed the highest refractory rate of 77.8%; furthermore, tumor involved bone tissues showed a higher refractory rate than those only involved soft tissues; finally, malignant tumors had worse outcomes than benign tumors.[25] On the other hand, these results demonstrated that benign tumors also persisted or recurred in some cases, which is consistent with previous studies.[169] In multiple regression analysis, this study found that female, spine tumors, bone tissue–involved tumors, malignant tumors, low preoperative serum phosphate levels, and high preoperative FGF23 levels were risk factors associated with refractory outcomes while preoperative serum FGF23 level had an area under the curve (AUC) of 0.7656 for discriminating refractory and remission outcomes.[25]

Serum phosphate is an easily accessible parameter to monitor surgery outcomes. We suggest that serum phosphate levels should be evaluated in consecutive 5 days right after surgery and repeated every 3–5 days until two successive normal results or 1 month after surgery to identify the outcomes. Once persistent or recurrent diseases develop, especially when the resected tumor turned out to be a non-PMTs according to histopathological examination, the diagnosis of TIO should be reconsidered. If TIO is still suspected, re-localize the responsible tumor following the stepwise localization process is recommended. The sensitivity of ^{99m}Tc-HYNIC-TOC to identify recurrent tumors was 86.7% in a retrospective study of 18 patients,[171] and there are also reports suggested that ^{68}Ga-DOTATATE-PET/CT was also capable to detect culprit recurrent tumors after octreotide scintigraphy failed.[172] Generally, about 80% of refractory patients successfully located suspicious tumors again, and reoperation still benefited these patients.[25, 145] Of note is that the remission rate of reoperations, which is approximately 50% according to one study, seems to be lower than primary operations.

Medical treatment

Therapy of TIO is directed first toward resection of the tumor. When complete resection of the causative tumor is not successful or not possible, medical treatment could lead to clinical improvement to a certain extent.

Conventional treatment

Conventional medical treatment is the supplementation of phosphate and active vitamin D (calcitriol or alphacalcidol).[173] The therapeutic goal of conventional medical treatment is to alleviate clinical symptoms, increase serum phosphate levels, normalize ALP, and maintain PTH in the normal range. Complete normalization of serum phosphate usually represents an overdose. As far as we know, there is no RCT or any prospective study concerning the optimum dose of phosphate and active vitamin D. We recommend a dose of 20–40 mg/kg/day (1–3 g/day for adults) for element phosphate and a dose of 20–30 ng/kg/day (0.5–1.5 μg/day for adults) for calcitriol. The equivalent dosage of alphacalcidol is 1.5–2 times that of calcitriol. Phosphate supplements

should be divided into 4–6 doses/day and titrated to the target dose over several days to weeks to minimized gastrointestinal side effects, such as abdominal discomfort and diarrhea. It is not necessary to get up in the night on the purpose of distributing the interval of each dose equally.[14,15,120]

FGF23 antibodies

Burosumab or KRN23, a fully human monoclonal antibody against FGF23, is the most promising drug in near future. Burosumab has been proved to be effective in reversing biochemical changes and improving symptoms in children and adults with XLH.[174–177] In a suspicious TIO case with elevated FGF23 concentrations and two DOTATATE PET/CT avid lesions, 70 mg/month of burosumab normalized serum phosphate after initiation and improved symptoms after 7 weeks.[178] Clinical trials of burosumab in patients with TIO are ongoing. Unpublished preliminary results suggested normalization of serum phosphate, improvement of histomorphometric indices, and alleviation of symptoms in 24–48 weeks of use.[179] However, if the drug is associated with increasing FGF23 levels or progression of the tumor in long term is unknown. Concerning the long-term effectiveness and safety, we recommend using burosumab only in patients with unresectable tumors, or for symptoms controlling purpose during the reduplicative tumor localization process in patients with undetectable lesions. The dosage of burosumab is different depending on the nations. The recommended initial dosage of burosumab for TIO is 0.5 mg/kg once every 4 weeks; round dose to the nearest 10 mg; and maximum dosage 2 mg/kg (not to exceed 180 mg) every 2 weeks. Dosage adjustment should be based on serum phosphate. Evaluate fasting serum phosphate monthly, measured 2 weeks postdose, for the first 3 months of treatment and as clinically necessary thereafter.

FGFR inhibitors

FGF receptor inhibitor suppresses of the downstream signaling of from Klotho-FGF receptor complex are also potential drugs to treat patients with TIO. A pan FGF receptor inhibitor BGJ398 and an inhibitor of mitogen-activated protein kinase (MAPK) PD0325901 are effective in Hyp mice.[73, 180] In humans, BGJ398 normalized FGF23 and phosphate levels and reduced tumor burden in two TIO cases.[181] Although promising, the efficacy of these drugs needs more evidence. Despite dose adjustments, tyrosine kinase inhibitor-related side effects led to infigratinib being discontinued after 18 months of treatment.[182]

Cinacalcet

Cinacalcet, a calcium-sensing receptor agonist, was reported to result in decreases in PTH and sustained increases in tubular phosphate resorption in patients with TIO.[183] However, it seems that hypercalciuria developed frequently, and evidence is scarce and inconsistently.[21, 135, 166] In a clinical study, the administration of calcimimetics agent cinacalcet to TIO patients led to a sustained increase in serum phosphate level and TRP while decreasing serum PTH and calcium. This result suggested the cinacalcet might be a useful adjuvant in the treatment of FGF23-mediated phosphate wasting disorders, and the phosphaturic effect of FGF23 was inhibited

by a decrease in serum PTH. However, this study also revealed that cinacalcet treatment in TIO patients for >70 days would increase serum FGF23 levels, and hypercalciuria developed frequently.[183]

Clinical outcome after treatment

The complications of conventional medical treatment include secondary or even tertiary hyperparathyroidism,[75] nephrolithiasis, nephrocalcinosis, and reduced renal function. Thus, renal function, PTH, serum calcium, 24-h urinary calcium, and renal ultrasound should be examined at baseline of treatment, and biochemical tests should be monitored every 3 months to adjust the medication dosage. During follow-up, usually, elevated PTH represents overdose of phosphate, elevated serum, or urinary calcium represents overdose of active vitamin D.

Other treatment

Ablative therapy has been used in patients with TIO who are neither willing nor qualified to undergo complete excision surgeries on tumors, with challenging anatomical tumor location, severe comorbid conditions.[184–190] It is a process using heat (microwave, ultrasound, laser, or radiofrequency), cold (cryoablation), or chemical agents (percutaneous ethanol instillation) to destroy tissues, performed under the guidance of multimodality imaging such as ultrasound and CT augmented by fusion of MRI, ^{18}FDG PET/CT, or ^{68}Ga-DOTATATE PET/CT, depending upon which modality best defines the tumor margins. Radiofrequency and cryoablation were used in most cases.[184–190] Among the present reported 13 cases treated with ablation, only one patient with a large and incomplete resected tumor failed,[187] while all the other patients reached biochemical resolution and clinical improvement a few days after ablation.[184–190] However, the high remission rate of current cases may result from publication bias, and the true effective rate is unknown due to the lack of long-term follow-up, head-to-head comparison studies and relatively large sample size studies. We recommend that ablation therapy should be used after careful consideration of patient condition and surgical risk.

Peptide receptor radionuclide therapy (PPRT) is an emerging method to treat neuroendocrine neoplasms.[191, 192] This therapy delivers highly localized radiation by targeting specific receptors (which are usually SSTR 2 and 5) on tumor cells.[192] In three cases from India, two of them recovered partially after PRRT using ^{177}Luttetium tagged DOTATATE.[57, 165, 193] Modest reduction in uptake on both ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT suggesting a favorable response.[57]

In cases of incompletely resected tumors, adjuvant radiotherapy has been used to avoid recurrence. However, there are insufficient data to support this practice.[120, 194] A few reports have provided evidence indicating the achievement of long and complete remission in patients with TIO in whom the positive margins of the resected tumor were treated with radiotherapy postoperatively, but other studies show lower disease-free survival rates.[195, 196]

Monitoring

Once the tumor causing TIO has been successfully removed, patients' symptoms improve

within days or weeks after surgery.[140, 197] An exacerbation of bone pain may occur in some patients and persist for several weeks, the underlying mechanism of which is still unclear.

Bone mineral density increases after tumor complete removal. Results from PUMCH show that BMDs of total hip and lumbar spine of patients after surgeries are increased by 30.9% and 49.3%, respectively, while among patients with the drug therapy the increase is 12.9% and 8.7% after a 6-month follow-up.[14] Minisola *et al*[120] observed a dramatic increase in the bone mineral density within 2–4 years after complete tumor resection. Colangelo *et al*[17] also demonstrated a striking increase of BMD values that peaked at 26.7 ± 6.5 months and then leveling off with the absence of further fractures.

Evidence-based studies that assess the best strategy to follow after the initial operation have not been carried out. In our experience, for patients with complete tumor removal, biochemical parameters, especially serum phosphate, should be measured initially every 6 months and then at yearly intervals with a DXA examination. The biochemical profile of patients should be fully re-evaluated in cases in which clinical symptoms suggest a recurrence. However, for patients who fail to locate the tumor and adopt a long-term medical treatment, the interval examinations for biochemical parameters, such as serum calcium, phosphate, and PTH, as well as urinary calcium should be shortened to every 3–6 months to adjust the drug doses and prevent the side effects.[121] Tumor localization in these cases should be repeated every 1–2 years, in hopes that a tumor may be more evident with time.[120, 121] The Diagnostic and management diagram of TIO is summarized in Supplementary Figure 3.

Summary

TIO is a rare metabolic bone disease that gradually devastates the quality of life of affected patients, but curable in the majority of cases with localized tumors by complete excision of causative tumors. The diagnosis, especially localization diagnosis is challenging. Knowledge of this condition is still restricted to a few specialized centers, leading to delay of diagnosis and appropriate treatment. In this consensus, we attempted to cover most features of TIO and aimed to guide the management of TIO. We hope that this consensus will reduce the gap in the management of TIO and improve the prognosis of patients with TIO.

There is still a far distance between the standard management of TIO and current evidence. In terms of diagnosis, we need to propose some specific and easy-obtained criteria to help making suspicious diagnoses quickly in primary health care institutions. For example, patients having “tetralogy of TIO” (bone pain, muscle weakness, chronic hypophosphatemia, and adult onset) could be suspected in the diagnosis of TIO. Besides, future studies should focus on the mechanisms of tumorigenesis and FGF23 overproduction. Understanding these processes will promote future non-surgical treatment targeted tumor since inoperable cases and incomplete excision are not uncommon. Finally, the improvement of novel drugs including burosumab, FGFR1 inhibitors would greatly expand treatment options of TIO in the future.

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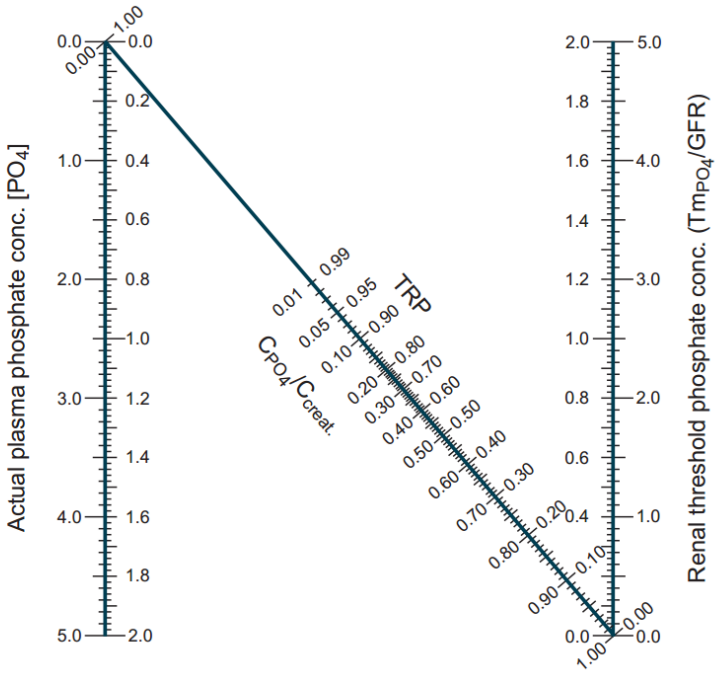
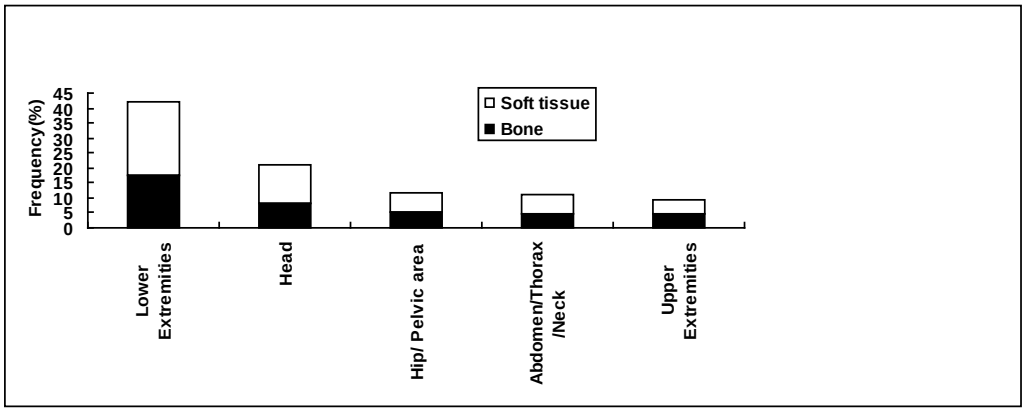
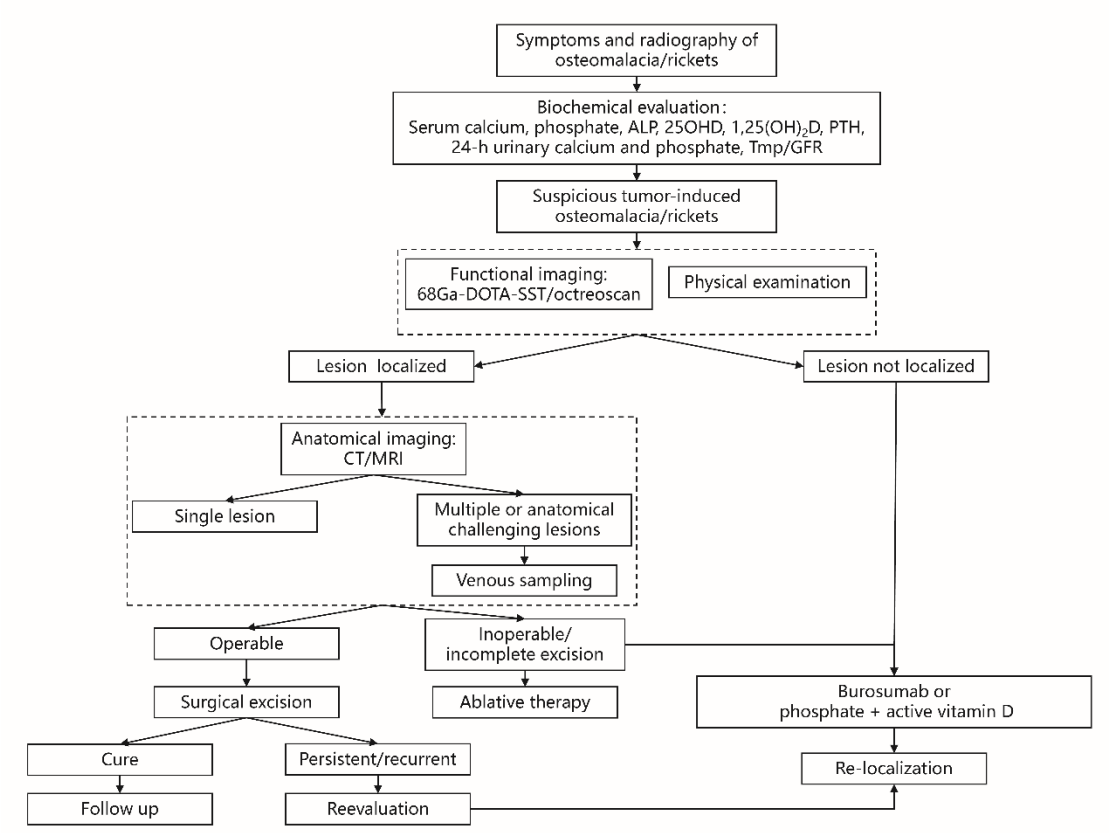


Supplementary Figure 1: Walton-Bijvoet chart. GFR: Glomerular filtration rate; TRP: Tubular reabsorption of phosphate.



Supplementary Figure 2: Frequency of tumors per region.[6]



Supplementary Figure 3: The Diagnostic and management diagram of TIO. $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; ^{68}Ga-DOTA-SST: ^{68}Ga-DOTA-conjugated-somatostatin-receptor-targeting-peptides; GFR: Glomerular filtration rate; TmP: Tubular maximum reabsorption of phosphate; TIO: Tumor-induced osteomalacia.

Supplementary Table 1: FGF23-related hypophosphatemic rickets/osteomalacia

Inherited forms of FGF23-related hypophosphatemic rickets/osteomalacia
XLH
ADHR
ARHR
Disease syndromes of FGF23-related hypophosphatemic rickets/osteomalacia
NF1
ENSs
FD/MAS
OGD
Acquired form of FGF23-related hypophosphatemic rickets/osteomalacia
TIO

ADHR: Autosomal dominant hypophosphatemic rickets or osteomalacia; ARHR: Autosomal recessive hypophosphatemic rickets or osteomalacia; ENSs: Epidermal nevus syndromes;

FD/MAS: Fibrous dysplasia/McCune-Albright syndrome; NF1: Neurofibromatosis type 1; OGD: Osteoglophonic dysplasia; TIO: Tumor-induced osteomalacia; XLH: X-linked hypophosphatemic rickets.