This is a pre-copyedited, author-produced version of an article accepted for publication in Endocrine Reviews following peer review. The version of record Salvatore Minisola, Seiji Fukumoto, Weibo Xia, Alessandro Corsi, Luciano Colangelo, Alfredo Scillitani, Jessica Pepe, Cristiana Cipriani, Rajesh V Thakker, Tumor-induced Osteomalacia: A Comprehensive Review, Endocrine Reviews, Volume 44, Issue 2, April 2023, Pages 323–353, is available online at: https://doi.org/10.1210/endrev/bnac026.

TUMOR-INDUCED OSTEOMALACIA: A COMPREHENSIVE REVIEW

Salvatore MINISOLA *[1] (000-0001-6625-0439), MD

Seiji FUKUMOTO *[2] (0000-0003-3610-3469), MD, PhD

Weibo XIA *[3] (0000-0001-7768-5536), MD

Alessandro CORSI[4] (0000-0001-6896-4509), MD, PhD

Luciano COLANGELO[1] (0000-0002-5835-9310)

Alfredo SCILLITANI[5] (0000-0001-9954-4187), MD

Jessica PEPE[1] (0000-0002-3088-0673), MD, PhD

Cristiana CIPRIANI[1] (0000-0002-0141-1202), MD, PhD

Rajesh V. THAKKER[6] (0000-0002-1438-3220), ScD

* These authors contributed equally to this work

[1] Department of Clinical, Internal, Anaesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

[2] Fujii Memorial Institute of Medical Sciences, Institute of Advanced Medical Sciences, Tokushima University, Japan

[3] Department of Endocrinology, Key Laboratory of Endocrinology of National Commission of Health, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. Beijing 100730, China

[4] Department of Molecular Medicine, Sapienza University of Rome, Italy

[5] Unità Operativa di Endocrinologia Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS)-"Casa Sollievo della Sofferenza"-Hospital, San Giovanni Rotondo, Foggia, Italy

[6] Academic Endocrine Unit, Radcliffe Department of Medicine, University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), Churchill Hospital, Headington, Oxford OX3 7LJ, UK

email addresses (in order)

salvatore.minisola@uniroma1.it

fukumoto-tky@umin.ac.jp

xiaweibo8301@163.com

alessandro.corsi@uniroma1.it

luciano.colangelo@uniroma1.it

alfredo.scillitani@gmail.com

jessica.pepe@uniroma1.it

cristiana.cipriani@uniroma1.it

rajesh.thakker@ndm.ox.ac.uk

Short title: Tumor-induced osteomalacia

Key words: Fibroblast growth factor, phosphaturic mesenchymal tumors,

43 osteomalacia, fracture, DOTA based imaging, burosumab.

44 Corresponding Author. S. MINISOLA, Department of Clinical, Internal,
45 Anaesthesiological and Cardiovascular Sciences, Sapienza University of Rome,
46 Rome, Italy. Via del Policlinico 155, 00161 Rome, Italy tel*393296340736
47 Reprint requests should be addressed to SM

48

49 R.V.T. receives funding from the National Institute for Health Research (NIHR)
50 Oxford Biomedical Research Centre Programme.

51

52 SM served as speaker for Abiogen, Bruno Farmaceutici, Diasorin, Kyowa Kirin,
53 UCB. He also served in advisory board of Eli Lilly, Kyowa Kirin, UCB. SF
54 received consulting fee Kyowa Kirin, Co., Ltd. Remaining authors declare no
55 conflict of interest.

56 Words count (Body of the paper) = 16,015

57 Figures = 7

58 Tables = 2

59 References = 323

60

ABSTRACT

Tumor-induced osteomalacia (TIO) is an ultrarare paraneoplastic syndrome due to overproduction of fibroblast growth factor 23 (FGF23), with profound effects on the morbidity of the patients affected. TIO is an underdiagnosed disease, whose awareness should be increased among physicians, for timely and proper management of the patients. Symptoms reported by patients with TIO are usually nonspecific thus rendering the diagnosis elusive, with an initial misdiagnosis rate of >95%. Biochemical features of TIO are represented by hypophosphatemia, increased or inappropriately normal levels of FGF23 and low to low normal circulating $1,25(OH)_2D$. Phosphaturic mesenchymal tumors are the pathological entities underlying TIO in most affected patients. There is now evidence that FN1-FGFR1 and FN1-FGF1 fusion genes are present in about half of tumors causing this paraneoplastic syndrome. Tumors causing TIO are often of small size and grow slowly. They can occur in all parts of the body from head to toe with similar prevalence in soft tissue and bone. There are a number of functional and anatomical imaging techniques utilized for tumor localization; 68Ga DOTA based technologies have the better sensitivity. Surgery is the treatment of choice; several medical treatments are now available in case of inability to locate the tumor or in case of incomplete

excision.

1) Definition

Tumor-induced osteomalacia (TIO) is an ultra-rare paraneoplastic syndrome characterized in the vast majority of cases by overproduction of fibroblast growth factor 23 (FGF23), most commonly by small phosphaturic mesenchymal tumors. FGF23 excess causes renal phosphate wasting and hypophosphatemia. The consequent inefficient bone mineralization is associated with musculoskeletal pain, reduced bone mineral density, disrupted trabecular microarchitecture and insufficiency fractures in the adulthood[1]. In children, growth retardation and growth plates expansion are the main clinical hallmarks [1].

In this Review, we will discuss various aspects of the disease, highlighting novel and consolidated aspects of epidemiology, pathophysiology, pathological findings and clinical aspects. We will also describe the portfolio of therapies available from surgery to new molecules. Finally, we will present future research goals to fill in the gap we still have in many aspects of this disorder.

2) Epidemiology: Prevalence, Incidence, Morbidity and Mortality

In recent years there has been an increasing number of publications on TIO.

This probably reflects, among other things, a better understanding of the pathophysiology of the disease, a raised awareness by clinicians and also the introduction on the market of new molecules to treat patients not amenable to surgery, or failing initial surgery or those in whom the disease recurs. In the face of this, the epidemiology of TIO has not been extensively investigated with a consequent paucity of papers in the literature. This is probably due to the fact that TIO is, by definition; an ultra-rare disease; in addition, the lack of a specific International Classification of Diseases diagnostic code further complicates the estimates of both incidence and prevalence.

There are two papers mainly addressing the issue of epidemiology of TIO. The first one is a survey carried out in Japanese hospitals [2]. The incidence of new TIO cases in Japan was estimated to be roughly the same as newly diagnosed X-linked hypophosphatemic cases (0.04 per 100.000 persons per year). Even though this was the first paper trying to address the issue of epidemiology of TIO, there were some biases that could undermine the validity of estimates obtained. For example, it is not clear from the paper how the Authors excluded that a patient could be double counted, because admission in more than one hospital; then, it is unclear how sampling and calculation of incidence accounted for the difference in duration of X-linked hypophosphatemia (XLH) and TIO, since the first one is a chronic condition while the majority of patients with TIO are amenable of surgical cure. In the

second paper, Abrahamsen and co-workers carried out an observational study querying the national Danish health registers. They found that the incidence of TIO in Denmark was below 0.13 per 100.000 person years for the total population investigated and 0.10 per 100.000 in adult-onset disease. The prevalence of TIO was estimated to be no more than 0.70 per 100.000 persons for the total population and 0.43 per 100.000 in adults. This study also underlines the rarity of the disease, that represents one of the biggest obstacles to its early diagnosis [3].

Concerning gender, the study of Abrahamsen et al., showed that patients with a possible diagnosis of TIO who have advanced imaging procedures and were taking vitamin D derivative were 40 % men and 60 % women, from a total population of 80 patients. Recently, Rendina and coworkers carried out a systematic review and individual patient's data analysis of 1725 patients with TIO. The diagnosis was made in 843 men (55 %) and 689 women (45 %). However, data regarding sex were missing in 193 TIO subjects [4]. Finally, TIO is very rare before the age of 18 even though sporadic cases have been reported in children as young as 3 years of age [5].

Recently there have been some attempts to better understand quality of life, morbidity and mortality in patients with TIO. Jerkovich and colleagues evaluated the clinical disease burden in a small group of patients with TIO (sample size of 8 patients) [6]. They found that the fatigue experienced by

patients with TIO was significantly higher compared to the general population ($p < .0001$). The physical summary measure of the SF-36 showed significantly lower values than those of the Argentinean control population with chronic conditions (mean 20.4 versus 45.9, $p < 0001$). According to the Brief Pain Inventory short form, patients with TIO have moderate average pain and the pain interferes severely with walking, general activities, work, and mood. Seven patients had a diagnosis of sarcopenia, four of which had severe sarcopenia. The conclusion was that patients affected by TIO have a poor Health Related Quality of Life in comparison with the general population. These data are very similar to those found in patients suffering from XHL [7].

Very recently, Minisola and coworkers [8], carried out a targeted literature review to describe the signs, symptoms and impacts of TIO and summarize the state of research on the burden of disease of this ultra-rare condition. They found that patients with TIO experienced a combination of outcomes including chronic pain, weakness, skeletal-related manifestations and limitations in mobility. Only a few studies ($n = 2/70$) analyzed the burden of TIO on the emotional wellbeing and on the work life of the patient. Patients with TIO present with a spectrum of signs and symptoms that impose a significant burden. The impact on the psychosocial wellbeing of patients should be further investigated, as this has been poorly researched so far.

In conclusion, the studies carried out so far, together with personal

authors' experience, point to emphasize the low quality of life of patients with TIO in relation to the clinical consequences of excessive FGF23 secretion. However, studies with high quality of evidence should be designed to further the understanding of the burden of disease of TIO from the patient's perspective [8]. Similarly, there is a need of well-designed studies to explore the short- and long-term impact of the disease on mortality, in respect to a control population. This investigation should be carried out both in patients surgically treated that completely recover from the disease and also in those not cured by but on long term medical treatment.

3) Pathophysiology

i. Control of serum phosphate level

Mineralization of bone and tooth progresses by deposition of hydroxyapatite crystals on osteoid proteins produced by osteoblasts [9]. Hydroxyapatite crystals are formed in matrix vesicles from calcium and phosphate ions. Chronic hypocalcemia and especially chronic hypophosphatemia can result in impaired mineralization causing osteomalacia. Serum phosphate level is regulated by intestinal phosphate absorption, glomerular filtration, renal tubular handling of phosphate and equilibrium between blood phosphate and that in intracellular fluid or bone [10]. Of these, renal handling of phosphate is the main determinant of serum phosphate levels in a chronic state.

Most of phosphate filtered through glomeruli is reabsorbed in proximal tubules. Several types of sodium-phosphate cotransporters are expressed in the brush border membrane of proximal tubules. Type 2a and 2c sodium-phosphate cotransporters are encoded by *SLC34A1* and *SLC34A3*, respectively, and PiT-2 encoded by *SLC20A2* are present in renal proximal tubules [11]. The expression of type 2a and 2c sodium-phosphate cotransporters are regulated by several factors including dietary phosphate, PTH and FGF23 [12]. PTH and FGF23 suppress the expression of these sodium-phosphate cotransporters and inhibit proximal tubular phosphate reabsorption. PTH suppresses the expression of *SCL34A1* and *SLC34A3* [13]. In addition, PTH enhances the internalization of type 2a and 2c sodium-phosphate cotransporters. Especially, PTH was shown to internalize type 2a sodium-phosphate cotransporter within minutes after administration [14]. FGF23 was also shown to have genomic and posttranslational effects on the expression of these sodium-phosphate transporters [15, 16].

Actions of FGF23

Human *FGF23* gene encodes a protein with 251 amino acids [17, 18]. After the cleavage of a signal peptide of twenty-four amino acids, full-length FGF23 with 227 amino acids is secreted. A part of FGF23 protein is proteolytically processed between 179Arg and 180Ser. This processing is mediated by

enzymes that recognize 176Arg-177His-178Thr-179Arg (R-X-X-R) motif like furin [19]. While the full-length of FGF23 shows the activities as shown below, the processed N-terminal and C-terminal fragments are inactive [20]. This indicates that the serum level of full-length FGF23 reflects FGF23 activities. Therefore, the serum level of full-length FGF23 and FGF23 activities can be modulated by both *FGF23* transcription and posttranslational modification of FGF23 protein. The attachment of O-linked glycan to 178Thr prevents the proteolytic processing of FGF23 and works to increase FGF23 levels [21, 22]. This attachment of O-glycan to 178Thr is initiated by UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase 3 encoded by *GALNT3* [21]. In contrast, phosphorylation of 180Ser accelerates the processing of FGF23 protein [23].

Osteoblasts/osteocytes are considered to be physiological producing cells of FGF23 [24-28]. Unlike other FGF family members, FGF19 subfamily members, FGF19, FGF21 and FGF23, has low affinity for heparin/heparan sulfate [29]. Because of this characteristic, FGF23 is not trapped in extracellular matrix around the producing cells and can enter systemic circulation. FGF23 binds to KLOTHO-FGF receptor 1 (FGFR1) complex in target tissues and activates signal transduction systems [30, 31]. Crystal structure of FGF23 and ectodomains of KLOTHO and FGFR1 indicates that KLOTHO is necessary for the binding of FGF23 to FGFR1 [32]. FGF23 suppresses the expression of type 2a

231 and 2c sodium-phosphate cotransporters in the proximal tubules [33]. In
232 addition, FGF23 inhibits the expression of *CYP27B1* which encodes 25-
233 hydroxyvitamin D [25(OH)D]-1α-hydroxylase and enhances that of *CYP24A1*
234 producing 25(OH)D-24-hydroxylase [33]. By these actions on the expressions of
235 vitamin D-metabolizing enzymes, FGF23 reduces serum level of 1,25-
236 dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2$D is a hormone that enhances
237 intestinal calcium and phosphate absorption. Overall, FGF23 reduces serum
238 phosphate by suppressing proximal tubular phosphate reabsorption and
239 intestinal phosphate absorption **(Figure 1).**

240 These physiological actions of FGF23 have been confirmed by
241 phenotypes of *Fgf23*-null mice and patients with hyperphosphatemic familial
242 tumoral calcinosis (HFTC). HFTC is a rare genetic disease characterized by
243 ectopic calcification especially around large joints. Three genes, *FGF23*,
244 *GALNT3* and *KLOTHO*, have been identified to be responsible for HFTC [25]. The
245 mutations in these genes induce impaired actions of FGF23. *Fgf23*-null mice
246 and patients with HFTC show hyperphosphatemia with enhanced proximal
247 tubular phosphate reabsorption and high 1,25$(OH)_2$D levels [25, 34, 35]. In addition
248 to hyperphosphatemia and high 1,25$(OH)_2$D levels, *Fgf23*-null mice also show
249 hypercalcemia and suppressed PTH levels all of which are considered to
250 suppress the expression *Cyp27b1*. However, the expression of *Cyp27b1* is
251 enhanced in *Fgf23*-null mice indicating the potent suppressive effect of FGF23

on the expression of this gene [34].

ii. Regulation of FGF23 production

Because FGF23 is a hormone that reduces serum level of phosphate and $1,25(OH)_2D$, it is plausible that phosphate and/or $1,25(OH)_2D$ affect FGF23 production and FGF23 levels. $1,25(OH)_2D$ was shown to enhance FGF23 production and increase FGF23 levels [36, 37]. Genomic region near *Fgf23* gene which mediates response to $1,25(OH)_2D$ was reported in *Fgf23* gene [38]. These results indicate that $1,25(OH)_2D$ transcriptionally enhances FGF23 production and there is a negative feedback loop between FGF23 and $1,25(OH)_2D$.

High phosphate diet is also reported to increase FGF23 levels both in human and rodents [39-41]. However, the mechanisms involved in phosphate-sensing by cells remain to be elucidated. Recently, it has been reported that the calcium-sensing receptor (CaSR), which binds to ionized calcium and activates downstream signal transduction systems [42], may also have a role in sensing changes in extracellular phosphate concentrations [43]. Thus, increases in phosphate concentrations were found to significantly inhibit CaSR activity via non-competitive antagonism and to be associated with rapid and reversible increases in PTH secretion from freshly-isolated parathyroid cells from humans and wild-type mice, but not those from mutant mice lacking the *Casr*. These findings indicate that the CaSR likely acts as a phosphate sensor in the

parathyroid glands to mediate the stimulatory effect of phosphate on PTH secretion [43]. Other reports have indicated the involvement of the FGFR - extracellular signal-regulated kinase (ERK) pathway in response to phosphate. High extracellular phosphate induced phosphorylation of ERK and osteopontin expression in osteoblastic MC3T3-E1 cells [44]. In addition, high extracellular phosphate induced phosphorylation of ERK and FGF receptor substrate 2α (FRS2α) in HEK293 cells which were prevented by silencing *Fgfr1* expression [45]. High extracellular phosphate was also shown to induce phosphorylation of ERK and FRS2α, and dentin matrix protein 1 (DMP1) expression in osteoblastic cells. The induction of DMP1 by high extracellular phosphate was inhibited by an FGFR inhibitor [46]. These results suggested that phosphate can transduce signals into cells via FGFR and modulate gene expression.

The involvement of FGFR - ERK pathway is also reported in the regulation of FGF23 production in the posttranscriptional regulation. High phosphate diet increased serum FGF23 levels in mice and enhanced expression of *Galnt3*, but not *Fgf23*, was observed in femur of these mice [47]. High extracellular phosphate induced *Galnt3* expression in osteoblastic UMR106 cells through FGFR1 - ERK pathway. Proteomic analysis of UMR106 cells stimulated by high extracellular phosphate identified FGFR1 as the only one receptor tyrosine kinase that was activated by high extracellular

phosphate[47]. In addition, deletion of *Galnt3* using *osteocalcin*-Cre prevented the increase of FGF23 in response to high phosphate diet [47, 48]. These results suggested that FGFR1 mediates the effect of phosphate on FGF23 production.

PTH was also shown to stimulate FGF23 production [49]. In addition to phosphate and calcium-regulating hormones, many factors including inflammatory cytokines, erythropoietin, iron deficiency, calciprotein particle, lipocalin 2, sclerostin, aldosterone and myostatin have been shown to enhance FGF23 production [50-57]. In contrast, several others such as insulin, insulin-like growth factor 1 and retinoic acid were shown to suppress FGF23 production [58, 59]. However, it is not established whether these factors have some role in the physiological regulation of serum phosphate and FGF23 levels. In addition, FGF23 was also reported to be produced by several extraskeletal tissues such as heart, artery, liver, and kidney[60-63]. Further studies are necessary to establish the physiological and pathophysiological significance of this extraskeletal FGF23 production.

iii. Possible mechanisms of FGF23 overproduction in tumors responsible for TIO

TIO is biochemically characterized by hypophosphatemia with impaired proximal tubular phosphate reabsorption. While hypophosphatemia is one of stimulators of 25(OH)D-1α-hydroxylase, serum 1,25$(OH)_2$D levels are usually low – low normal in patients with TIO[64]. These features are explained by

315 excessive actions of FGF23 and mimicked by phenotypes of *FGF23*-transgenic
316 mice [65]. FGF23 was identified as a causative factor for TIO and FGF23 levels
317 have been reported to be elevated in most patients with TIO [18, 66]. There are
318 reports of patients with typical features of TIO whose FGF23 levels are normal
319 [67]. In addition, several other factors such as matrix extracellular
320 phosphoglycoprotein (MEPE), soluble frizzled-related 4 and FGF7 have been
321 reported to be produced by tumors causing TIO and have phosphaturic
322 actions [68-70]. However, blood levels of none of these proteins, except FGF 7 [71],
323 have been reported to be increased in patients with TIO. While it is possible
324 that there are cases of hypophosphatemic osteomalacia caused by other
325 factors than FGF23, these cases seem to be rare.

326 In addition to TIO, there are several hypophosphatemic diseases
327 caused by excessive actions of FGF23 with similar biochemical features to
328 those of TIO. These include X-linked hypophosphatemia (XLH) and autosomal
329 recessive hypophosphatemic rickets 1 (ARHR1) [72-75]. XLH is caused by
330 inactivating mutations in *phosphate-regulating gene with homologies to*
331 *endopeptidases on the X chromosome (PHEX),* and ARHR1 is caused by
332 inactivating mutations in *DMP1*. However, it is not clear how mutations in
333 these genes result in high FGF23. Microarray analysis of bone obtained from
334 a mouse model for XLH, referred to as *Hyp* and due to deletion of the 3' region
335 of *Phex* [76], and *Dmp1*-null mice indicated that signals in the downstream of

FGFR are stimulated in these mice [77]. In addition, deletion of *Fgfr1* from *Hyp* mice decreased FGF23 production in bone and serum FGF23 level [78]. These results suggest that FGFR1 is involved in the overproduction of FGF23 in genetic hypophosphatemic diseases.

There are also several reports suggesting the involvement of FGFR1 in the overproduction of FGF23 in tumors responsible for TIO. Lee et al. found nine out of fifteen phosphaturic mesenchymal tumors (PMTs) responsible for TIO harbored *fibronectin (FN1)-FGFR1* fusion gene by several methods including next generation sequencing, RT-PCR and fluorescence in situ hybridization [79]. In a subsequent paper, they also identified *FN1-FGF1* fusion gene [80]. In these two papers, the frequency of *FN1-FGFR1* and *FN1-FGF1* fusion genes were 42 % (21/50) and 6 % (3/50), respectively. The presence of these fusion genes was mutually exclusive. Therefore, these results indicate that the fusion genes are present in about a half of tumors responsible for TIO. The function of the fusion proteins has not been clearly demonstrated. However, FN1-FGFR1 protein is considered to facilitate the activation of FGFR1 [79]. FN1-FGF1 fusion protein is proposed to be secreted and bind to FGFR1 as a ligand [80]. If these fusion genes work to activate FGFR1, it is possible that the signals from FGFR1 is involved in the overproduction of FGF23 as discussed above **(Figure 2).**

KLOTHO was reported to be expressed in a tumor responsible for TIO

by RNA sequencing [81]. Subsequent analysis by immunohistochemistry and/or RT-PCR indicated that KLOTHO was expressed in 69% of tumors (9/13) [81]. These tumors were negative for *FN1-FGFR1* or *FN1-FGF1* fusion genes. FGFR1 was reported to be expressed in 82% (45/55) of PMTs [80]. These results suggest that KLOTHO-FGFR1 complex is present in at least some tumors without the fusion genes and this complex is activated by FGF23. The phosphorylation and therefore activation of ERK were demonstrated in most tumors responsible for TIO again suggesting the activation of signals from FGFR1 [81]. The frequent expression of KLOTHO in PMTs without the fusion genes was confirmed by another study [82]. They also found the expression of βKLOTHO in some tumors which is a homologous protein to KLOTHO [82]. βKLOTHO has been shown to work as a co-receptor for FGF19 and FGF21 together with FGFRs [83]. It has not been shown that βKLTOHO can transduce signals from FGF23.

Taken together, FGFR1 was proposed to be involved in the regulation of FGF23 production in response to phosphate. In addition, FGFR1 is shown to be activated in bone of model mice of FGF23-related hypophosphatemic diseases. Furthermore, several reports suggest the activation of FGFR1 in tumors responsible for TIO. This activation of FGFR1 could be involved in the overexpression of FGF23 in these tumors. It is also possible that the activation of FGFR1 contributes to the growth of tumors because inhibitors of FGFRs have been developed for solid tumors [84]. However, tumors causing TIO are

usually slow-growing tumors. There is not enough evidence that shows the involvement of FGFR1 activation in the growth of tumors responsible for TIO.

In contrast, there are several questions to be answered in the future research works. First, it is not known whether the expression of fusion genes and KLOTHO is present in cells producing FGF23 while there are a variety of cells in tumors responsible for TIO. Second, the function of the fusion gene products has not been clearly demonstrated. Third, even if FGFR1 is involved in the enhanced FGF23 production, fusion genes and expression of KLOTHO are not observed in all tumors causing TIO. There seem to be other mechanisms that result in FGF23 overproduction.

4) Pathological features of Phosphaturic Mesenchymal Tumors

Prader and colleagues were the first to appreciate a neoplasm, a putative "giant cell reparative granuloma of bone", as the cause of osteomalacia [85]. Since then, TIO was reported in association with different benign and malignant mesenchymal tumors including vascular tumors, chondroma, osteoblastoma, soft tissues or sinonasal "hemangiopericytoma", giant cell tumor of bone and osteosarcoma [67, 86-88]. In 1972, Evans and Azzopardi [89] and Olefsky and colleagues [90] were the first to note that TIO-associated tumors shared distinctive histological features that make them unique. This was made clear

399 in 1987 by Weidner and Santa Cruz [91], who coined for these tumors the term
400 of “Phosphaturic Mesenchymal Tumor, mixed connective tissue variant”, and
401 definitely established in 2004 by Folpe and colleagues in their seminal study[87].
402 Since 2013 Phosphaturic Mesenchymal Tumors (PMTs) are recognized as
403 specific entity in the WHO Classification of Tumors of Soft Tissue and Bone
404 as “morphologically distinctive neoplasms that produce tumor-induced
405 osteomalacia in most affected patients, usually through production of
406 fibroblast growth factor 23” [92]. The demonstration of fusion events involving
407 the *FN1-FGFR1/FGF1* genes [79, 80] supports the nosologic identity of PMTs (see
408 section on *Possible mechanisms of FGF23 overproduction in tumors responsible*
409 *for TIO*). The pathological features of PMTs have been recently reviewed [88].
410
411 *i. Histology, immunohistochemistry and ultrastructure of PMT*
412 PMTs most often involve the soft tissues of extremities and the appendicular
413 skeleton and less frequently craniofacial bones and paranasal sinuses [1, 67, 86-88,
414 93-104]. Exceptionally these tumors are evaluated through incisional biopsy due
415 to the potential for tumor cell seeding [1, 105]. When excised, their gross
416 presentation is virtually not specific (**Figure 3).** Calcifications and
417 hemorrhages can be appreciated on cut surface. Histologically (**Figures 4 and**
418 **Figure 5 a and b**), PMTs are composed of bland, round-oval to spindle cells
419 (i.e., the source of FGF23 and other “phosphatonins”) associated with a florid

vascularization consisting of small, arborizing capillaries, branching vessels (hemangiopericytoma-like) or dilated vascular spaces (cavernous hemangioma-like) and with an overt excess of extracellular matrix that typically calcifies in an unusual “grungy” manner. Osteoclast-like Tartrate-Resistant-Acid-Phosphatase (TRAP)-positive multinucleated giant-cells, “fibro-histiocytic” cells, microcystic spaces, myxoid, chondromyxoid, hyalinized extracellular matrix, also closely resembling primitive cartilage or osteoid, peri-tumoral woven bone formation (in particular in soft tissue tumors) and mature adipocytes (in particular in sinonasal tumors) can also be detected [87, 88, 92]. In the soft tissues, PMTs may be challenging to resect for their tendency to infiltrate into surrounding tissues [88]. In bone, PMTs may permeate the inter-trabecular spaces and produce abundant osteoid-like matrix mimicking an osteosarcoma [88]. Compared to PMTs involving soft tissues and bone, sinonasal PMTs commonly contain few, if any, calcified matrix and multinucleated giant-cells and often show thick-walled vessels and fascicles of vaguely myoid-appearing spindle cells that may mimic other vascular or perivascular tumor [88, 101, 102, 104, 106]. Overall, the relative proportions of neoplastic cells, blood vessels, matrix, dystrophic calcification, multinucleated giant-cells and fat are variable from case to case [67, 87, 88]. In the jaws, an epithelial component may coexist [98, 103, 107] and for these tumors the terminology of "phosphaturic mesenchymal tumor, mixed epithelial, and connective tissue type" has been proposed [103].

However, as FGF23 mRNA is not expressed in the epithelial component, it is reasonably interpretable as odontogenic epithelium entrapped within the tumor rather than a component of the neoplastic tissue [88, 97, 103].

Immunohistochemistry has limited value in the recognition of PMTs. Most studies have shown predominantly a "vimentin-only" phenotype [87, 88, 91]. Indeed, neoplastic cells have been reported to be variably immunoreactive for alpha-Smooth Muscle Actin, Muscle Specific Actin, PGP9.5, S-100, CD34, NSE, CD68, Synaptophysin, Dentin Matrix Protein-1, Somatostatin Receptor-2A, D2-40, ERG, CD99, Bcl2, SATB2, CD56, EMA, DOG1, Periostin, FGF23, Klotho and FGFR1 [80, 87, 88, 96, 103, 104, 107-120]. None of these markers is both highly sensitive and specific. However, part of them may suggest some osteogenic differentiation of the neoplastic cells which in turn might reflect the physiological role of osteogenic cells in FGF23 production [25-28]. In addition, the immunoreactivity of the neoplastic cells for Somatostatin Receptor-2A well accounts for the utility of somatostatin receptor-targeted imaging in tumor localization (*see section on Localization studies*) [112, 121, 122]. According to Houang and colleagues [112], immunoreactivity of the neoplastic cells for SSTR2A is highly sensitive but not specific for the diagnosis of PMT and that increased specificity may be obtained through the immunohistochemistry for both SSTR2A and FGF23. Additional immunophenotypic features were highlighted by Agaimy and colleagues[116], according to which the co-expression of SATB2, SSTR2A, ERG

462 and CD56 may support the diagnosis of PMT, in particular when “difficult-to-
463 diagnose” and not associated with TIO.

464 In few studies, PMTs have been examined by Transmission Electron
465 Microscopy (TEM) [91, 108, 111, 113, 123-125]. In two cases, one from bone and the other
466 from soft tissues (**Figure 5 c-e**), we observed neoplastic cells showing irregular
467 nuclei with inconspicuous nucleoli and with variable amounts of mitochondria,
468 lysosomes and lipid vacuoles, scattered cisternae of rough endoplasmic
469 reticulum and small vesicles. The extra-cellular matrix was composed of
470 collagen fibrils and granular material and, in particular in the soft tissue
471 tumor, contained abundant calcifications. These findings overlapped those
472 previously described. Interestingly, as in some of the previously reported
473 cases [108, 111, 113, 124], dense core, membrane bound neurosecretory-like granules
474 were detected in the neoplastic cells of the soft tissue PMT.

475

476 *ii. “Non-phosphaturic” variant of PMT*

477 Tumors with morphological features overlapping those of “phosphaturic”
478 PMTs and demonstrable expression of FGF23 have been also reported in the
479 absence of TIO [67, 87, 88, 100, 115, 116, 118, 119, 126]. The *FN1-FGFR1* fusion has been
480 demonstrated in some of these tumors [100, 115, 119]. This variant may reflect
481 tumors with clinically unrecognized TIO, tumors identified before any
482 manifestation of osteomalacia, secretion of insufficient or inactive amount of

FGF23 by neoplastic cells or occurrence of the tumor in patients with some type of compensatory mechanism [67, 88, 118, 126]. As observed by Florenzano and colleagues [97], “FGF23 excess could eventually develop” if a recurrence occurs. For this reason, it is reasonable in these patients to monitor phosphate levels after the histological diagnosis.

iii. Multifocal and malignant PMT

Although commonly solitary and benign, PMTs may be either multiple or malignant [67, 87, 88, 99, 100, 118, 127-138]. Multiple tumors have been reported to show histology, immunophenotype, FGF23, and fusion gene expression and invasion potential comparable to those of the solitary counterpart[118]. As observed by Li et al [95], “there is no consensual histopathological criteria for nonmetastatic malignant PMTs.” Histologically malignant PMTs are recognized for high cellularity, high nuclear grade, necrosis, elevated mitotic activity, high Ki67 index and p53 expression and are associated with recurrences, distant metastases and adverse outcome [67, 87, 88, 99, 116, 118, 127-130, 133, 138]. However, the identification of an otherwise typical benign PMT component is critical in the distinction of malignant PMTs from other sarcomas of soft tissues and bone [88]. FGF23 expression has been demonstrated in both the primary tumor and in the metastasis [127]. Metastasis from histological benign

PMT [138, 139] and malignant “non-phosphaturic” variant of PMT [132] have been described as well.

iv. Pitfalls in the pathologic diagnosis of PMT

Many different mesenchymal tumor types have been reported as the cause of TIO [67, 86-88]. However, as clearly established by Boland and colleagues [67], “it seems quite clear that the overwhelming majority of these” tumors, if not all, “represent misdiagnosed PMT, which were not recognized owing to the rarity of these tumors and lack of familiarity by pathologists with their morphological spectrum”. Detailed criteria for the pathological differential diagnosis of PMT from other mesenchymal tumors have been previously reported [87, 88].

Most PMTs are resected for the treatment of clinically established TIO. Thus, the clinical scenario provides a robust contribution in the correct pathological diagnosis (i. e, PMT). When clinically unsuspected, awareness of the unique heterogeneous histological spectrum and demonstration of either FGF23 expression (at mRNA or protein level or both) and/or molecular *FN1-FGFR1/FGF1* fusions should allow for the distinction of PMT from the wide variety of benign and malignant neoplasms with which PMTs may be confused [87, 88]. However, some pitfalls have to be kept in mind. First, anti-FGF23 antibodies are not currently available in all pathology laboratories. In addition,

524 they have been reported to have “questionable specificity” [88] and not to be
525 “reliable enough” to diagnose PMT[94]. Immunoreactivity for FGF23 has been
526 observed in control conditions and often very focally "limiting its diagnostic
527 utility particularly on small biopsies”[112]. The definition of the positive staining
528 is also crucial. In some studies[112, 114], only the dot-like pattern (i.e., distinct
529 punctate perinuclear staining), and not the diffuse cytoplasmic staining, has
530 been considered as positive. For these reasons, FGF23 mRNA-based assays, as
531 Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) or RNA Scope
532 Chromogenic In Situ Hybridization (CISH), have to be preferred [67, 88, 99, 104, 115, 118,
533 119, 126, 127]. Both assays are highly sensitive but, compared to RT-PCR, CISH shows
534 greated specificity and allows preservation of tissue architecture and
535 selective demonstration of FGF23 mRNA expression by the neoplastic cells[88,
536 127]. This is extremely important in bone located PMT for the identification of
537 the specific FGF23-expressing cell population (neoplastic *vs* normal osteogenic
538 cells) that cannot be unequivocally established through RT-PCR [67, 88, 126, 127]. In
539 addition, in the "phosphaturic mesenchymal tumor, mixed epithelial, and
540 connective tissue type" of the jaw, the epithelial component has been reported
541 to be immunoreactive for FGF23 but negative for FGF23 mRNA through CISH
542 assay thus suggesting that they represent entrapped dental remnants rather
543 than a tumor cell component [88, 103]. Second, even though very rarely, PMTs may
544 be negative for FGF23 expression [67, 88, 127] and cases with typical PMT and

545 osteomalacia and normal FGF23 serum levels have been also described [67, 127, 140].
546 In these circumstances, other "phosphatonins" should be considered for the
547 development of TIO [28, 67-70, 88, 97, 104, 141-144]. Third, as *FN1-FGFR1/FGF1* fusions lack
548 in about 50 % of PMTs [67, 79, 80, 88], their absence is not sufficient to rule out PMT.
549 Last but not least, *FN1* rearrangements are not specific for PMT. For example,
550 they have been recently reported in synovial chondromatosis and in soft tissue
551 chondromas [145]. As a consequence, if Fluorescent ISH (FISH) for *FN1*
552 rearrangements is used in the pathologic work-up, the results need to be
553 integrated with the clinical, laboratory, imaging and histological data. In
554 addition, FISH studies have demonstrated that the *FGFR1* rearrangement can
555 be detected in a minority of tumor cells, reflecting the abundance of non-
556 neoplastic cells within the PMT and raising the possibility of a false-negative
557 result [67, 79, 88].
558
559 *v. Hypophosphatemia caused by increased FGF23 in clinico-pathologic settings*
560 *other than hereditary hypophosphatemic disorders and PMT-related TIO*
561 In addition to hereditary hypophosphatemic disorders (ADHR, XLH, ARHR
562 types I, II and III) [75], FGF23-related hypophosphatemia may also occur in
563 completely different clinical-pathological settings including non-hematologic
564 [67, 88, 127, 146-154] and hematologic [155-157] malignant tumors and genetic syndromes
565 namely Neurofibromatosis (NF) [67, 88, 158-161], Polyostotic Fibrous

566 Dysplasia/McCune-Albright Syndrome (PFD/MAS) [26, 67, 75, 88, 162-164] , Cutaneous
567 Skeletal Hypophosphatemia Syndrome (CSHS) [75, 164-168] and Osteoglophonic
568 Dysplasia (OGD) [75, 169]. In some of the patients with malignancy, the neoplastic
569 cells have been convincingly shown to be the source of FGF23 based on their
570 immunoreactivity for FGF23 or expression of FGF23 by RT-PCR[152, 153, 157].
571 Interestingly, in one patient with disseminated ovarian serous carcinoma,
572 osteomalacia and elevated serum level of FGF23, neoplastic cells were
573 reported to be negative for FGF23 mRNA by CISH thus suggesting alternative
574 mechanisms for the development of the syndrome [67, 88, 127]. Among the genetic
575 syndromes, at least in type-I NF and in particular in PFD/MAS, the elevated
576 FGF23 serum level has been related to the disease burden [26, 88]. As *RAS*
577 mutations are detectable within the bone lesions [166], Ras/Mitogen-Activated
578 Protein Kinase pathway seems to have a strong effect on the production of
579 FGF23 [164] and bone is the usual source for FGF23 [25-27], the bone lesions
580 themselves have been thought to be the source of excess FGF23 production in
581 CSHS [166]. In OGD, a rare skeletal dysplasia caused by activating mutation of the
582 *FGFR1* gene and characterized by rhizomelic dwarfism, craniosynostosis,
583 midfacial hypoplasia, prognatism, teeth abnormalities and non-ossifying
584 fibroma-like bone lesions, elevated FGF23 level leading to hypophosphatemia
585 can occur, likely from local production within the bone lesions [75, 169]. According
586 to Florenzano and colleagues [97], these genetic conditions associated with

587 excess of FGF23 “should be designated by their underlying syndrome”.

588 A TIO-like syndrome has been described also in two children with
589 extra-hepatic biliary atresia [100] and associated with intravenous infusion of
590 some forms of iron preparations [170-172] and, possibly, with chronic alcohol
591 consumption [173]. In the two patients with extra-hepatic biliary atresia, the
592 syndrome resolved after orthotopic liver transplantation and in one of them
593 affected hepatocytes were immunoreactive for FGF23. In iron infusion-
594 induced FGF23-related hypophosphatemia, it has been clarified that the final
595 rate-limiting step to determine the serum intact FGF23 level is the post-
596 translational O-glycosylation initiated by *N*-acetylgalactosaminyltransferase 3
597 [21, 47]. Further studies are in progress to confirm the association of TIO-like
598 syndrome and chronic alcohol consumption [173].

599

600 *vi. Histological aspects of skeletal tissue in TIO*

601 Bone biopsy after sequential administration of tetracyclines and its
602 histomorphometric evaluation can be part of the clinical work-up in the
603 patients with suspected TIO *(see section on Distinctive laboratory findings)*. As
604 expected [174], in the cases in which it has been performed [175-177], light microscopy
605 revealed increase in osteoid parameters relative to mineralized bone including
606 osteoid volume, surface and thickness and fluorescence microscopy a range
607 of severity from reduced or undetectable distance between double labels to

608 no tetracycline uptake reflecting the defective bone matrix mineralization (i.e.,
609 osteomalacia). Processing for plastic embedding [117, 178] of samples from a PMT
610 involving bone [117] will let to demonstrate osteomalacia in the intra- and peri-
611 tumoral bone trabeculae (**Figure 4 i**).
612
613 **5) Clinical**
614 *a) Presentation: symptoms and signs*
615
616 *i. Skeletal symptoms*
617 Symptoms reported by patients with TIO, such as for example bone pain, are
618 usually nonspecific thus rendering the diagnosis elusive, with an initial
619 misdiagnosis rate of up to 95.1 % [179]. In any case, symptoms are rarely related
620 to the tumor itself, wherever it is located, because of its small size. An
621 exception might be the location in the head region when tumors are located
622 within the nasal sinuses [97]. In this circumstance about half of the patients (44.1
623 %) experience local symptoms [180] such as obstruction or bleeding.
624 Symptoms are often present for months or years before the diagnosis
625 and surgical cure of the disease. Generally, the longer the putative disease
626 duration, the worse the bone involvement [179, 181], often confining the patient to
627 a wheelchair. As a consequence of the delay in diagnosis, patients frequently
628 have severe disability, including thoracic and spinal deformities at time of

diagnosis, as pectus carinatum and kyphosis [97]. Furthermore, hip fractures have been reported in retrospective analysis as a complication of the disease in 34 out of 144 patients (23.6 %) [179]. Height loss is a quite common finding; an average height loss reduction of 7.8 ± 4.7 cm has been reported [179]. Occasionally, due to severe thoracic deformities respiratory insufficiency may occur.

In adults, the most frequent symptom is bone pain. A retrospective study of 144 patients with TIO [179], reported that 99 % of them suffered skeletal pain. The pain may derive from the location of the tumor in the skeletal tissue or as a consequence of fractures (80 % of patients) or may be related to the underlying malacic condition.

In the few cases of TIO reported during childhood, rickets was the predominant clinical manifestation together with growth retardation [1].

Clinical and radiological presentation of patients with TIO often overlap those of patients with spondyloarthritis or other rheumatologic disorders, such as for example disc herniation or vertebral deformities. Lack of specificity underlies the high misdiagnosis rate [182]; for example, a total of 240 case-times of misdiagnoses occurred in the 144 TIO patients [179]. Patients are often seen also at oncological and psychiatric centers.

The skeletal manifestations of TIO are almost the same as those described in osteomalacia due to other causes. X-rays usually show

osteopenia, coarse trabeculae, Looser's zones, insufficiency fractures and bowing of long bones [183, 184]. Looser's zones or "pseudo fractures" represent the radiological hallmark of osteomalacia and reflect skeletal fragility; they occur late in the natural history of the disease [184]. Typically, they are transverse lucencies with sclerotic borders traversing partway through a bone, usually perpendicular to the involved cortex, (with a width range of 1 mm to 1 cm) with symmetrical distribution. Contrary to what is generally believed, they are often located in non-weight-bearing bone, following and corresponding to blood vessels in contact with bone[185]. Although inter-individual differences exist, they are usually found at the ischiopubic area, iliac wings, tibia, radius, fibula or lateral scapula [185]. From a clinical point of view, they are usually painful [184]. X-rays images may appear as "poor quality" radiographs. This is due to the large amount of unmineralized osteoid that appears as indistinct and poorly defined from trabecular bone [184].

Stress fractures may be part of the skeletal involvement in tumor-induced osteomalacia; they were often characterized as "slow-healing" in this context [186]. However, these lesions do not deserve further investigation because of spontaneous healing following tumor resection. Indeed, one year following successful removal, the disappearance of the lesion with its replacement by a sclerotic area deforming the cortical profile of the bone was described in a long term-follow up [187].

Bone densitometric values are severely reduced especially in patients with long standing TIO [181]. Following the cure of the disease a striking increase of bone mineral density is observed. From the histological point of view, this is due to the huge mineralization of the osteoid tissue accumulated, particularly in those with the long-standing unrecognized disease [117]. Recently an assessment of bone microstructure and density in the axial and peripheral skeleton by high resolution peripheral computed tomography, trabecular bone score in addition to bone mineral density was reported for the first time in a large cohort of patients with TIO[188]. The Authors concluded that disease duration, mobility, history of fracture, and biochemical variables were correlated with bone microarchitecture deterioration. Impaired bone microarchitecture evaluated by high resolution peripheral computed tomography was also previously documented in a small series of 6 [189] and 10 [190] TIO patients, respectively.

ii. Non-skeletal symptoms

Regardless of the site of tumor development, there are common symptoms related to severe hypophosphatemia and not related to the presence of tumor itself [1]. In fact, weakness is a presenting symptom both in cases of tumors originating from skeletal regions [191], as well as in those originating from extraskeletal sites. In particular, muscular weakness due to the reduction of

692 intracellular adenosine triphosphate, has been reported in 65 % to 77 % of
693 patients [179, 180]. As a result, considering both the muscle and the skeletal
694 involvement, the patients may develop severe disability and difficulty in
695 walking by the time the disease is identified [117].

696 In some cases, a subcutaneous mass may be detectable through a
697 diligent physical examination when tumor originates from musculoskeletal
698 region. Patients therefore should be asked about the occurrence of new
699 “lumps” or “bumps” [192] to identify the culprit tumor. In a retrospective case
700 series, in 21 out of 144 patients (14.6 %) a local lump was responsible of the
701 disease [179].

702 A number of studies have been published focusing on the
703 pathophysiological consequences of FGF23 excess in renal function. Increased
704 urinary phosphate excretion is an independent risk factor for the development
705 of nephrocalcinosis, defined as the deposition of calcium crystals in the renal
706 parenchyma and tubules, or nephrolithiasis i.e., kidney stones. Although
707 nephrocalcinosis has been reported in 30 -70 % of pediatric patients with X-
708 linked hypophosphatemia [194] (a congenital disorder that is analogous to TIO),
709 there are no published data regarding the prevalence of nephrocalcinosis or
710 kidney stones in TIO patients.

711 However, the long-term conventional treatment with active vitamin D
712 metabolites and oral inorganic phosphate salts, in combination with

longstanding hyperphosphaturia, may cause adverse events in the kidney as hypercalciuria, nephrocalcinosis, and nephrolithiasis. Furthermore, the development of secondary or tertiary hyperparathyroidism is a well-known complication of long-standing treatment with oral phosphate. Indeed, an increasing number of reports have been published reporting the coexistence of hyperparathyroidism and oncogenic osteomalacia [195, 196].

In the past years, FGF23 has been reported as an independent risk factor for mortality and cardiovascular disease. In particular, FGF23 levels were independently associated with left ventricular hypertrophy in a chronic kidney disease cohort [197]. In this context, a study evaluated the potential role of FGF 23 in patients with FGF23-related hypophosphatemic rickets/osteomalacia [198] as an etiologic factor of hypertrophy, using the Sokolow-Lyon or Cornell criteria on electrocardiogram, or the left ventricular mass index by means of echocardiogram. The overall group was composed of 24 patients, of which 13 had TIO. Mean values of ventricular mass index, Sokolow–Lyon voltage, and Cornell product were all within the reference ranges. Concerning ventricular mass index, only two male patients with TIO had higher values than the reference range. Their Sokolow–Lyon voltage, and Cornell criteria were all within the reference ranges and they did not have chronic kidney disease. It is therefore unlikely that in patients with TIO, the heart may represent a target organ of excess FGF23 secretion [198].

Although TIO is an extremely rare disease, the possibility of malignant PMTs must be recognized. In these clinical situations, symptoms depend on the localization of metastasis, determining, for example, respiratory failure as a consequence of lung metastasis [133].

b) Distinctive laboratory findings

The hallmark biochemical features of TIO are represented by persistent low serum phosphate levels, due to renal phosphate wasting, and inappropriately normal or low $1,25(OH)_2D$ values [1].

The normal level of serum phosphate ranges from 2.5–4.5 mg/dL in adults (0.8 mmol/L to 1.45 mmol/L; to transform mg in mmol divide by 0.0259); thus, a serum phosphate level below 2.5 mg/dL is considered a condition of hypophosphatemia and should be investigated. In particular, a moderate hypophosphatemia is defined when serum phosphate level is within 1.0–1.7 mg/dL (0.4–0.5 mmol/L), while severe hypophosphatemia is considered when serum phosphate is lower than 0.9 mg/dL (0.3 mmol/L). Another point that should be emphasized derives from the observation that the normal ranges for phosphate and renal phosphate handling are different in children from adults[199]. This should be taken into account when investigating children under 18 years of age. Recently reported case series of TIO patients, diagnosed at tertiary care, academic centers or following

national surveys consistently show reduced values of serum phosphate. For example, mean serum phosphate levels of 1.3 ± 0.4 mg/dL have been reported in a case series from Italy[200] and median serum phosphate levels was 1.4 mg/dL (range from 1.2 to 1.6) in patients from South America [201]. Mean serum phosphate levels were 0.50 ± 0.13 mmol/L [202], 1.74 ± 0.35 mg/dL [2], 0.48±0.13 mmol/L [179] in patients from India, Japan and China, respectively.

Although moderate hypophosphatemia should be considered the distinctive laboratory hallmark of TIO, the finding of renal phosphate wasting is fundamental for establish the diagnosis. The most accurate way to evaluate the renal phosphate wasting is given by the calculation of the tubular maximum phosphate reabsorption per glomerular filtration rate (TmP/GFR), as explained in the diagnosis section. Normal values TmP/GFR are 2.5-4.5 mg/dL; in TIO patients the values are always below the reference range [203]. To calculate the TmP/GFR, urinary phosphate and creatinine should be measured as well as serum creatinine and phosphate levels. In particular, the second morning urine collection in patients fasting for 12 hours should be over 2 hours, with blood drawn at any time during this collection while the patient continues to fast. Another possibility is to calculate the percent tubular reabsorption of phosphate from a random simultaneous sample of blood and urine (% TRP). This value should also below the normal range for supporting the diagnosis of TIO. When serum phosphate levels are normal, the TRP

normal range is 85–95 %. In conditions of reduced serum phosphate values, the expected physiological response is an increase in tubular reabsorption of phosphate to values higher than 85–95 %, which are not seen in patients affected by TIO. The value of TmP/GFR can be calculated using a nomogram [203], while % TRP can be calculated with the following formula TRP=1 - (Serum creatinine X Urine phosphate)/ (Urine creatinine x Serum phosphate). Both TmP/GFR and % TRP can be calculated also using an online free calculator.

In patients with TIO, renal phosphate wasting is caused by the high levels of FGF23, which could be considered another distinctive laboratory findings in TIO. The pathogenetic role of FGF23 was associated with TIO approximately 50 years after the description of first case of TIO described in 1947 [204]. The best laboratory method to measure FGF23 still remains a matter of debate.

In humans, part of the full-length FGF23 (intact FGF23: iFGF23) undergoes a post-transcriptional cleavage thus generating, N-terminal and C-terminal FGF23 fragments with presumably no physiologic function, while intact FGF23 is considered the biologically active form of the hormone [20]. Laboratory measurements are usually classified into those measuring the intact molecule and those detecting the carboxy-terminal (C-terminal) fragment of FGF23. Indeed, FGF23 could be measured in 2 formats of enzyme-linked immunosorbent assays: a C-terminal assay measuring both full-length

and cleaved C-terminal fragment of FGF-23 [205] and intact assays of FGF23 [66] (iFGF23) requiring the N-terminal and C-terminal portion of the processing sites of FGF23 to detect only full-length uncleaved FGF23. Imel et al. reported a higher sensitivity of iFGF23 in TIO patients compared with C-terminal assay of the hormone [206]. As no international standard for iFGF23 and cFGF23 are available, it is currently not possible to standardize the assays, thus nowadays it impossible to assess the best FGF 23 method to detect TIO patients.

Whichever method is used, an elevated or unsuppressed level of serum FGF23 is reported in TIO patients [207-209]. In the literature, there are methods that report different normal ranges that are not always comparable [2, 66, 210, 211]. For example, a new chemiluminescence enzyme (CLEIA) method to detect FGF23 was compared to one of the most used that detects iFGF23 with an enzyme linked immunosorbent assay (ELISA) kit (KAINOS Laboratories, Tokyo, Japan) [66]; This new kit yielded lower FGF23 values when compared with the previous assay [212].

Although most reported patients with TIO have clearly elevated serum FGF23 levels, approximately sixteen TIO patients with normal FGF23 levels have been described since the first observation of the disease in the literature [2, 140, 201, 212-220]. A number of possible explanations have been put forward for this finding of apparently “normal values”. Firstly, it is possible that in these patients, FGF23 levels could have been misinterpreted due to the use of

incorrect reference values. Another hypothesis, although less likely, is that another phosphaturic hormone could be involved in the development of hypophosphatemia. However, in case of hypophosphatemia unrelated to FGF23, the level of the hormone should be low range. Therefore, the finding of FGF23 values in the upper normal range should be considered "inappropriately normal" and thus not affecting the diagnosis of TIO. A similar situation can be seen in hypercalcemic patients with PTH values in the upper third of normal range. Considering all of the above issues, head- to-head studies for improving the diagnostic accuracy of FGF23 in patients with TIO, comparing C- terminal with iFGF23 assays, are needed.

Concerning other parameters of mineral metabolism, serum calcium levels are within the normal range, as well as 25(OH)D provided that there is an adequate supply of the vitamin. PTH levels are within the normal range or sometimes higher due to low $1,25(OH)_2D$. Serum alkaline phosphatase levels as well as other markers of bone remodeling, are generally elevated; the degree of increase generally correlates with the degree of bone involvement.

c) Metabolomics

Recently, together with the well-known biochemical features of the disease, metabolomics has also been studied in patients affected by TIO [221]. Metabolomics refers to a large-scale study of metabolites that are directly

involved in the biochemical activity of a specific disease. The goal of metabolomics study is not only to optimize the diagnosis, but also to characterize the pathogenesis of the disease and possibly to find new targets for therapy.

In TIO patients, the first global metabolomics analysis was carried out in a sample of 24 male and 8 female patients with a mean age of 43.6 years [221]. By means of liquid chromatography–tandem mass spectrometry–based metabolomics, these patients were studied at different time points. Specifically, they were assayed at initial diagnosis and after tumor resection (1 to 3 days after successful surgery) and were matched with 32 healthy control subjects. The novelty of this study is the discovery of a metabolic pathway found perturbed in patients with TIO. This pathway mainly included arachidonic acid metabolism, fatty acid and lipid metabolism, as well as sphingosine and sphingosine 1 phosphate metabolism. In particular, five oxylipins, 4-hydroxydocosahexaenoic acid (4-HDoHE), leukotriene B4 (LTB4), 5-hydroxyeicosatetraenoic acid (5-HETE), 17-hydroxyeicosatetraenoic acid (17-HETE) and 9,10,13-trihydroxy-octadecenoic acid (9,10,13-TriHOME) were the top ranked metabolites able to discriminate TIO patients from healthy controls. Thus, the authors suggested that the combination of these oxylipins may help for diagnosis. As shown by receiver operator curve analysis, this panel of oxylipins reached a high sensitivity and specificity for TIO prediction

[221] (AUC = 0.95, CI = 0.82-1). After tumor resection, the expression of these biomarkers tended to decrease toward the levels found in healthy controls, but only the differences of 5-HETE and 17-HETE, were statistically significant ($p < 0.05$).

It is important to emphasize that the aim of metabolomics analysis is not only to improve the diagnosis but also to describe the metabolite pathways involved in a specific disease in order to promote a better understanding of the disease development. In this context, an interpretation of these data is that the role of these oxylipins in TIO pathogenesis, is mainly related to chronic inflammation. However, it is not certain if the tumor induced chronic inflammation, and thus a dysregulation of the oxylipins, could be considered as an epiphenomenon, or a dysregulation of the oxylipins related to chronic inflammation is a contributor of the development of the tumor [222]. In particular, both 5-HETE and LTB4 have been reported to play essential roles in the inflammation [223, 224] which is a significant risk factor for others tumor development [225]. In addition, LTB4 and 5-HETE can stimulate proliferation and suppress apoptosis in several types of cells [226-229]. More specific might be the role of LTB4. Indeed, it induces VEGF-mediated angiogenesis in vivo and high vascularization is one of the histological features found in TIO [230, 231]. Thus, upregulation of LTB4 might partially explain the enhanced angiogenesis that exists in TIO tumors. Of interest, the DHA

derivative 4-HDoHE was accumulated in TIO patients that were previously demonstrated to inhibit angiogenesis, tumor growth, and metastasis [232]. This finding of higher levels of 4-HDoHE, compared to controls, might possibly be the result from feedback regulation levels.

These new metabolomics findings should be interpreted with caution, because the possible influence of inflammation cannot be ruled out as a potential confounding factor that links the oxylipins pathway and TIO pathogenesis. Moreover, the presence of fractures in TIO due to osteomalacia could initiate an acute inflammatory response and could also be considered as a bias in analyzing the data [233]. Timing of analysis could also be important in this setting, and it is possible that the study of metabolomics, not only in the short-term postoperative (1-3 days) period, but also after few months after surgery could bring more information. Because this is the first comprehensive study of metabolomics in patients with TIO, other metabolomics studies are needed in the future.

d) Tumor Localization

Tumors causing TIO are often of small size and grow slowly. They can be localized in all parts of the body from head to toe with similar prevalence in soft tissue and bone [4] and in particular in head and neck and extremities [4, 93, 186]. The commonest tumor localizations were lower extremities (59.6 %)

902 followed by head and neck (24.0 %), torso (9.4 %) and upper extremities (6.9 %)
903 in a study where data of 287 patients with TIO were analyzed [234]. Asking the
904 patient for the occurrence of new lumps or bumps along with an accurate
905 physical examination with particular attention to the oral cavity and
906 extremities, could allow the identification of the small tumors. Indeed, in this
907 way, the identification of the tumor in 14.6 % of a Chinese series [179] and in a
908 recent review in 6.7 % has been reported [4].

909 After the accurate physical examination, a stepwise approach has been
910 recommended as a far as the utilization of different imaging techniques,
911 firstly employing the functional imaging then the anatomical ones. Since such
912 tumors are commonly of small size and often occur in sites that are not
913 included in the standard field of functional (e. g., FDG- PET/CT, octreo-
914 SPECT-CT, Gallium-68 PET-TC) or anatomical studies (e.g., CT, MRI), and
915 searching for these tumors should include the whole human body from vertex
916 to toe paying attention also to upper limbs.

917

918 *i. Functional imaging*

919 The main functional techniques take advantage of the expression with variable
920 degrees of somatostatin receptors (SSTRs, mainly SSTR subtype 2) on the
921 membrane of cells of tumors which allow, with SSTR scintigraphy imaging, the
922 identification of the tumors using somatostatin receptor analogs [121, 122].

However, the expression of these receptors is not specific for tumors causing TIO since they are expressed also from other neuroendocrine tumors as well as non-neuroendocrine neoplasms (e. g. lymphomas, breast cancer, thyroid cancer). Radiolabeled SSTR analogs can be used with single photon emission computed tomography (SPECT) or positron emission tomography (PET) for identifying tumors.

Octreotide, a synthetic octapeptide analog of somatostatin with a special binding affinity to SSTR2 has been conjugated with ^{111}In; typically, scans using such substance are commonly referred as *octreoscan*. It can be combined with SPECT, so providing 3D information, and eventually also combined with a co-registered computed tomography (SPECT-CT) in order to produce a better anatomical picture. Whole-body octreoscan SPECT-CT should include head, neck and limbs, sites that are commonly excluded; however, this combination is time consuming so that the acquisition of tomographic images is often restricted to areas of tracer uptake on planar imaging [235]. ^{99m}Tc-hydrazinonicotinamide (*HYNIC*)-*octreotide* is a ^{99m}Tc labeled somatostatin analog that has been utilized for performing whole-body SPECT-CT scan for localizing tumors causing TIO. It has been reported to have a sensitivity of 86.3 % and a specificity of 99.1 % for detecting tumors [148] and is less time consuming than octreoscan. Pitfalls of both these tracers are mainly represented by the uptake of inflammatory tissues and, for example, a cold,

octreoscan in patients may show the uptake by nasal mucosa a site where tumor causing TIO is not infrequently discovered [235].

Gallium-68 (^{68}Ga) is a positron-emitting radionuclide that can be linked to a chelator (DOTA) that can link a somatostatin analog peptide such as Tyr-3-octreotate (TATE) or 1-Nal3-octreotide (NOC) or Tyr-3-octreotide (TOC). These peptides have a different affinity profile for the SSTR receptors. Although, DOTATATE, DOTANOC and DOTATOC have been successfully utilized for localizing tumors causing TIO, DOTATATE is the preferred one for the higher affinity for the SSTR2 which are mainly expressed on the cell surface of tumors causing TIO. The *^{68}GaDOTATATE* can be combined with positron emission tomography and eventually also combined with a co-registered CT. Whole-body ^{68}GaDOTATATE PET-CT has been reported to have a sensitivity of 100 % (even though, other Authors have reported slightly lower values, see below) and high specificity (91 %) with an accuracy for localizing tumors causing TIO of 97.7 % [236]; it has been reported to be superior to octreo SPECT-CT in localizing the tumor [216]. This can be explained by the higher affinity of ^{68}GaDOTATATE for SSTR2 than octreotide [237] and for the better spatial resolution of PET in respect to SPECT. Since the expression of SSTRs is not specific for tumors, but can be expressed for example on inflammatory cells [238] or in sites of fractures [239], the tracer uptake observed with octreoscan as well as ^{68}GaDOTATATE should also be characterized by anatomical imaging

965 such as CT or Magnetic Resonance Imaging (MRI) [235].

966 Fluorine-18 (^{18}F)-AIF-NOTA-octreotide (^{18}F-OC) combined with PET and
967 CT, ^{18}F-OC PET/CT is a useful technique in detecting the SSTR-expressing
968 tumors. It has been utilized for localizing tumors causing TIO with promising
969 results [240].

970 ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is not considered a specific tracer; it
971 enters the cells expressing glucose transporters. ^{18}F-FDG uptake in the cells is
972 linked to their metabolic activity. Contrast-enhanced *^{18}F-FDG PET-CT* is a
973 technique often used for oncological indications based on the metabolic
974 activity of tumors and has shown a relatively high sensitivity for localization
975 of tumors causing TIO [241]. Pitfalls due to false positive uptake should be taken
976 into account; for example, infections [242] and also insufficiency fractures often
977 seen in patients with osteomalacia can show detectable ^{18}F-FDG uptake [243]. The
978 sensitivity of ^{18}F-FDG PET-CT is about 67 % and lower than octreoscan (83 %)
979 or ^{68}GaDOTATATE (90 %) [199, 234]. The lower performance of ^{18}F-FDG PET-CT could
980 be due to the low metabolic activity of tumors causing TIO [234], while
981 ^{68}GaDOTATATE after binding to the SSTR receptors is internalized thus
982 causing higher accumulation in tumor cells [199]. However, although ^{18}F-FDG PET-
983 CT has a lower sensitivity in identifying tumors than octreoscan or
984 ^{68}GaDOTATATE [205, 214], it can be complementary to somatostatin analog imaging
985 since sometimes tumors causing TIO are identified with ^{18}F-FDG PET-CT and

not with somatostatin analog imaging [186]. Moreover, ^{18}F-FDG PET-CT has been suggested to have a role in predicting possible recurrence of TIO [244].

^{99}mTc-sestamibi scintigraphy (MIBI) with SPECT and also with SPECT-CT modalities have been suggested for localizing tumors causing TIO [245]. However, they are considered the least accurate technique among the functional ones in localizing such tumors [1].

In conclusion, ^{68}GaDOTA SSTR PET/CT having the better sensitivity for detection of culprit tumors in TIO should be used as first line functional imaging technique [199].

ii. Anatomical imaging

Contrast enhanced MRI is indicated for confirming the presence and the extension of the tumor, already suspected after functional techniques [235] and also to plan subsequent surgery [1, 105]. Contrast enhanced CT has the same indications of MRI. Although in general inferior to MRI, because MRI better characterizes soft tissue and bone [235], CT could be useful in specific situations, i. e., in defining bone tumors causing TIO [1].

iii. Venous sampling

The sequence of functional and subsequent anatomical imaging is in general able to localize the tumor causing TIO. However, there are some cases where

other modalities are indicated to increase the degree of diagnostic certainty (i. e., multiple suspected lesions are found; the suspected lesion is located in a region where the surgical treatment can be associated with a high degree of potential morbidity). In these cases, selective venous sampling with plasma (or serum, depending on the assay) FGF23 measurement has been utilized for confirming the tumor causing TIO [246]. Recently, a case report has been described in which intraoperative FGF23 assay has been utilized, to confirm tumor resection in a case of possible double localization of the tumor[117].

iv. Fine needle aspiration

Some authors suggested to perform aspiration of the lesion with measurement of FGF23 on eluate and eventually cytological exam [246, 247] in suspected lesions localized with functional and anatomical imaging techniques. However, this technique has been discouraged for the potential tumor cell seeding [1, 105].

Finally, there are patients in whom, the tumor cannot be localized even after an extensive diagnostic work-up. In a retrospective survey recently carried out in Japan, the percentage of patients in whom the tumor was not identified was as high as 37.5 % [248]. In these particular cases, a periodic follow-up is recommended.

v. Diagnostic approach and differential diagnosis

Diagnosis of TIO is based on the clinical evaluation of patients, laboratory findings and imaging studies for tumor localization. As for many rare disorders, one of the critical points is to consider TIO in the differential diagnosis in a patient with the typical clinical presentation, namely a progressive musculoskeletal disorder characterized by pain, insufficiency fractures, and eventually disability. As the first clinical presentation is often nonspecific, diagnosis may be delayed and patients could be treated for other musculoskeletal disease, as well as rheumatological, neurological or psychiatric disorders. Misdiagnosis at presentation is reported in 87.5-95 % of cases [248, 249].

Assessment of patient's medical history should focus on the onset of symptoms that could date back to several years before [1]. Musculoskeletal pain is progressively worsening and unresponsive to common analgesics; it could be associated with fractures or pseudofractures, height loss, and skeletal deformities [250]. Muscle weakness is commonly observed and disabling. Walking impairment may result and lead patient to progressive disability with the use of wheelchair and eventually to be bedridden[248]. Table 1 summarizes the main disorders to consider in the differential diagnosis of TIO.

The hallmark of diagnosis that allows to differentiate TIO from many other conditions is the measurement of serum phosphate levels (Table 1).

Hypophosphatemia is defined as serum phosphate levels < 2.5 mg/dL (0.8 mmol/L) [251]. In the setting of hypophosphatemia and progressively worsening musculoskeletal ailment, patients' interview allows to infer many important information. It should be focused on past medical history, dietary and lifestyles habits, family history, and drug exposure. The proposed diagnostic algorithm to be implemented in clinical practice for the evaluation of patients with suspected TIO is as follows (**Figure 6)**. The presence of clinical manifestation (diarrhea, constipation, abdominal pain, weight loss, etc.) and/or laboratory findings of malabsorption syndrome should be carefully investigated (Table 1) [252]. Other causes of hypophosphatemia, such as nutritional deficiencies or low or absent sun exposure (e. g., patients with skin cancer, institutionalized subjects, use of clothes covering a significant skin area for cultural or religious tradition, etc.) should be investigated.

Assessment of family history should focus on the presence of inherited forms of phosphate or vitamin D-related disorders. As far as medications causing hypophosphatemia (intravenous iron, cisplatin, ifosfamide, azathioprine, tenofovir, adefovir, and valproic acid) [251], it is important to consider the opportunity of discontinuing the drug with the involvement of the specialist/s in charge of the patient and identify alternative therapies.

Routine laboratory assessment should include serum albumin adjusted calcium (where available, serum ionized calcium), creatinine, PTH, 25(OH)D,

1,25$(OH)_2$D, 24-hour urinary calcium and creatinine to exclude primary hyperparathyroidism and vitamin D deficiency. If all these were negative, the next step is to calculate the tubular reabsorption of phosphate (TRP) and/or the maximum tubular reabsorption rate for phosphate (TmP)/glomerular filtration rate (TmP/GFR). Such evaluation is determinant to assess renal phosphate wasting that is highly increased in TIO. Hypovitaminosis D should be corrected before TRP and TmP/GFR evaluation. Phosphate and creatinine are measured from random blood sample and urinary collection for TRP and the following formula is applied: 100 x [1 – (urinary phosphate/urinary creatinine) x (serum creatinine/serum phosphate)]. Tubular reabsorption of phosphate values range from 85% to 95 % in normal subjects [251]. Fasting blood sample and 2-hour morning urinary collection are needed for TmP/GFR calculation. The Walton & Bijvoet nomogram or an algorithm may be applied [203, 253]. Normal TmP/GFR values are age and gender-dependent [253]. Both TRP and TmP/GFR are reduced in TIO; hence, normal findings and/or increased TRP (> 85-95%) exclude the diagnosis of TIO. In the last case, focus should be posed on reduction in phosphate intake or malabsorption [251].

If TRP is < 85-95 % and/or TmP/GFR values are reduced for age and sex, an FGF23-related disorder is likely and FGF23 levels should be measured. Commercially available immunoassays use chemiluminescence (CLIA), CLEIA, or one- and two-steps enzyme linked immunosorbent assay (ELISA) methods

[254]. They measure intact FGF23 (iFGF23) or the sum of iFGF23 and C-terminal FGF23 and are used in most countries only in the research setting, an exception being, for example, represented by Japan [251, 254]. Absolute reference interval of FGF23 levels are not available; notwithstanding, it has been determined that FGF23 levels are not influenced by sex nor by age in adults, but rather by dietary phosphate intake and renal function[254]. Assay specific reference values for FGF23 are provided by the manufactures [254]. Additionally, specific cut-off serum phosphate and FGF23 values for the diagnosis of FGF23-related hypophosphatemia have been established for two assays[254].

Low FGF23 levels in the setting of increased phosphate wasting exclude TIO and indicate the presence of a non FGF23-related disorder **(Figure 6).** In this situation, the Fanconi syndrome should be considered by assessing urinary wasting of electrolytes, uric acid, amino acid, bicarbonate, glucose and other substances and blood gas analysis to exclude metabolic acidosis **(Figure 6).** When the Fanconi syndrome is suspected, causes of the acquired form should be investigated, such as all the possible causes of acute tubular necrosis (e. g. exposure to heavy metals, infections, such as Legionella Pneumoniae, light chain deposition disease, amyloidosis) (Table 1) [211]. When negative, the hereditary forms of FGF23-independent renal phosphate wasting, such as the hereditary Fanconi syndrome or the hereditary hypophosphatemic rickets with hypercalciuria should be excluded by genetic testing [251].

Normal or elevated FGF23 levels are diagnostic of an FGF23-related disorder causing hypophosphatemia. In this context, it is important to consider the presence of chronic kidney disease when evaluating serum FGF23, whose levels may increase even in mild stages. Hereditary forms of FGF23-related phosphate wasting should be excluded by genetic testing in specific clinical settings.

Young age at the onset of symptoms, growth retardation, bowing, dental and ear abnormalities reported by the patient or family members are typical determinants of hereditary disorders [251, 253]. The mutations to be investigated, according to the specific clinical suspicious, are those in the phosphate-regulating endopeptidase homolog X-linked (PHEX, X-Linked hypophosphatemia, XLH), FGF23 (autosomal dominant hypophosphatemic rickets, ADHR), dentin matrix acidic phosphoprotein 1 (DMP1, autosomal recessive hypophosphatemic rickets, ARHR, type 1), and ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1, ARHR, type 2) genes [251, 253]. Other genetic disorders to be considered in the differential diagnosis of FGF23-related hypophosphatemia include PFD/MAS (Table 1), a non-inherited disease caused by post-zygotic activating mutations of the alpha subunit of the stimulatory G protein encoded by the *GNAS* gene [26, 164] . In MAS, *café-au-lait* spots and the autonomous hyperfunction of various endocrine organs with precocious puberty, Leydig cell hyperplasia, thyroid abnormalities, and

GH excess are associated with FD lesions of bone (Table 1) [164, 255]. Apart MAS cases with very early neonatal onset [256] , FD lesions represent the most severe phenotypic expression of the disease because of bone pain, fractures, and deformities [164, 255, 257-259].

The radiological evidence of focal lytic, mixed or sclerotic lesion with internal ground-glass matrix is essential to suspect the diagnosis [255, 260].

Finally, other rare hereditary diseases casing hypophosphatemia and rickets are: CSHS, characterized by diffuse epidermal or melanocytic nevi; OGD, characterized by abnormal bone growth causing craniofacial abnormalities, dwarfism, and multiple teeth abnormalities; hypophosphatemic rickets with hyperparathyroidism, characterized by elevated Klotho, FGF23, and PTH levels (Table 1) [211, 251].

In the context of the typical clinical features and hypophosphatemia associated with low (or low normal) $1,25(OH)_2D$ concentrations and elevated FGF23 levels, the absence of the aforementioned clinical phenotypes and negative family history orient towards the diagnosis of TIO **(Figure 6),** the next step should be tumor localization. Again, past medical history and physical examination may be determinant in some cases. A positive medical history for tumors potentially associated with TIO, such as prostate adenocarcinoma and colon cancer, should be considered in the evaluation of screening tests for possible tumor relapse. Clinical examination may detect the presence of

painful or unpainful masses.

Functional and anatomical imaging studies are important in the localization of the tumor. The first step is to perform a DOTA scan (^{68}Ga-DOTATATE PET-CT) if available (Figure 6). Other approaches include a total body nuclear medicine study, preferably a single-photon emission computed tomography (SPECT), a SPECT-CT, a positron emission tomography (PET), or PET-CT [1, 250]. Somatostatin analogs, such as octreotide, pentetreotide, diethylenetriaminepentaacetic conjugate of octreotide, or other derivatives of octreotide bound to radionuclides (^{111}In – octreoscans, or ^{68}Ga) are employed in these studies [1, 250]. The DOTA-scan use the DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTATATE and DOTANOC as bifunctional chelators linking the ^{68}Ga to the somatostatin analogue and may be considered the gold standard for PMTs localization [261]. In particular, the ^{68}Ga-DOTATATE PET-CT, that is successfully employed in the diagnosis and staging of tumors expressing somatostatin receptors, such as pancreatic neuroendocrine tumors, demonstrated high sensitivity in the detection of PMTs owing to its affinity to the somatostatin receptors type 2 (SSTR2) [250, 262]. It is superior to octreoscans and to the fluorodeoxyglucose (^{18}FDG) PET-CT [1, 250]. The last technology represents an alternative when the somatostatin receptor nuclear medicine studies are not available or a complementary study when the octreoscans are not conclusive [1].

The algorithm for localization of the tumor sustaining TIO integrates the use of anatomical imaging technologies in association with functional tests. The contrast-enhanced MRI or CT allow to obtain anatomical details of the lesion and its contacts with the surrounding structures thus providing a valid guide for surgical resection.

Rarely, venous sampling of the area/s where the tumor has been localized by functional and/or anatomical imaging studies may be needed for confirming the diagnosis of PMTs or characterize multiple lesions [1, 250]. Blood is collected via a catheter and FGF23 levels are measured [1].

6) Therapy

The majority of TIO tumors are benign and single foci, and the surgical resection of PMT is the first choice once the tumor is accurately located by functional and anatomical images. In case the tumor is not localized, multifocal, unresectable, or malignant, then other alternative or adjuvant therapies besides surgery are recommended. The conventional medicines are neutral phosphate and active vitamin D preparations (e.g., alfacalcidol and calcitriol). Although this replacement therapy does not cure the disease, it may nevertheless alleviate the symptoms and help to seek opportunities for other treatments. Recently other targeted therapies have emerged, such as the anti-

FGF23 monoclonal antibody, burosumab, which is reported to be safe and effective in improving objective indicators and symptoms of TIO (Table 2).

a. Surgical treatment

i. Surgical principle

Compared with other types of hypophosphatemic rickets/osteomalacia which need long-term medical therapy, TIO is a curable disease in most cases. Complete tumor resection is the only definitive treatment, so surgery should always be the first-line therapy when possible [1, 97]. Although most culprit tumors are benign, TIO can persist or recur when residual tumor tissue exists, which could also happen due to the undetectable dissemination of tumor cells during biopsies [1, 105, 200]. Thus, complete tumor resection requires wide margins, and tumor biopsy should be performed with more caution in the diagnostic workup.

The evidence about the specific resection margin distance is deficient. In a recent study of 5 patients having soft tissue tumors with irregular borders, which are suspected to be infiltrative, recurrence did not occur in all patients who were treated with 1-cm-wide margin resection, but in one who underwent exact marginal tumor excision [263]. Since the infiltration depth was approximately 0.5-2 mm for these tumors, the preferred surgical margin for

irregular soft tumors is at least 1 cm [263]. On the other side, for tumors with regular boundaries and fibrous capsules, marginal resection seems to be sufficient [263-265]. Special attention should be paid to the identification and protection of local nerves, blood vessels, muscles, fascia, ligaments, and other important anatomical structures to avoid secondary damage in the context of complete resection [265]. 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 [264, 266]. Although there is no head-to-head trial, bone tumor resection appeared to be more effective than curettage [264]. So, tumor resection combined with total joint arthroplasty [267] or prosthesis reconstruction may be the optimal surgical method to cure TIO caused by bone tumors. However, these surgical approaches are often associated with greater morbidity attributed to dysfunction of extremities and prosthesis-related problems [264]. In general, the operative principle is to resect the culprit tumor completely with the fewest damages. Since the causative tumor can be located at any sites of the whole body, the optimal resection margin distance in different situations needs to be clarified in future studies.

ii Surgical outcome

The outcome of surgical treatment largely depends on the site of the culprit tumor and the surgeon's experience. Based on published data, refractory cases,

including both persistent and recurred ones, have been reported with a combined incidence of 0-57 % [87, 93, 116, 131, 134, 180, 186, 191, 202, 268-272]. In most cases, the residual or recurrent tumors were located at the original site, suggesting that the initial resections were incomplete, even if the surgeries were obedient to the recommended protocol by removing all visible tumors with wide margins [264]. In a recent study of 230 patients with TIO, 24 patients did not have immediate remission and 18 patients relapsed after the primary surgery, representing a non-response rate of 10.4 %, a recurrence rate of 7.8 %, and a combined refractory rate of 18.2 % [95]. Female, tumors on bone, spine tumors, malignant tumor, lower preoperative serum phosphate level, and higher preoperative serum FGF23 level are risk factors of refractory disease [95]. To our knowledge, there is no well-established method to predict the postoperative outcome. Since there are emerging promising alternative treatments to the surgery, in the future studies, it is important to classify the patients who are suitable for surgery to minimize the risk of undesirable prognosis.

The diagnosis of TIO should be reassessed if persistent or recurrent diseases arise, especially if the histological analysis revealed a non-PMT appearance of the excised tumor. If TIO is still suspected, the stepwise localization technique should be repeated to re-localize the causative tumor in the same way of newly diagnosed TIO. In a retrospective study of 18 patients, ^{99m}Tc-HYNIC-TOC had a sensitivity of 86.7 % for detecting recurring

tumors [273], and ^{68}Ga-DOTATATE-PET/CT may detect culprit recurrent tumors when octreotide scintigraphy failed [274]. The culprit tumors could be identified in approximately 80 % of refractory patients, and reoperations were still beneficial to these patients [95, 264]. It's noteworthy that repeated operations appear to achieve lower remission rates than first operations, by around 50 % [95]. Therefore, the indication of operation should be prudently determined in refractory patients, since the best operation procedure is still uncertain.

Treatments for patients with multifocal tumors [135, 136], malignant PMTs [95], metastatic diseases [132, 138, 139, 146, 154, 275-279], childhood onset [280-284] , and rare causes of TIO (e.g., secondary to malignant tumors instead of PMTs, such as prostate cancer [146], lung cancer [285], colon adenocarcinoma [149], renal carcinoma [150], ovarian cancer [151], lymphoma [286]) are often not successful, and in these cases controlling the primary disease should take priority if TIO is secondary to malignant tumours.

iii Postoperative recovery

Once the TIO-causing tumor is successfully removed, the circulating level of FGF23 drops rapidly in hours, while the phosphate and $1,25(OH)_2D$ concentrations gradually increase, and typically returns to the normal level within 5 (2-16) days [93]. Patients' symptoms begin to improve within a few days or weeks [93, 218, 287], but the complete relief may take several months [181]. Bone

mineral density could also increase in response, revealed by the study of PUMCH, in which the BMD of total hip and lumbar spine increased by 30.9 % and 49.3 % respectively after surgeries, whereas only increased by 12.9 % and 8.7 % in conventional drug-treated patients after a 6-month follow-up [94]. Following total tumor resections, Minisola *et al* [1] observed a considerable increase in bone mineral density within 2-4 years, and the BMD values peaked at 26.7±6.5 months and then leveled off with no further fractures in the study of Colangelo *et al* [181]. Hungry bone syndrome manifested by hypocalcemia and bone pain is the main postoperative complication, and calcium plus vitamin D supplementation is of necessity in this case [288].

b. Medical treatment

Although surgery is the only established, definitive treatment for TIO patients, medical treatments are critical when the causative tumors are not localized, multifocal, or unresectable. If the serum phosphate level is not normalized immediately or permanently after the surgery, the alternative medical therapy is recommended. Long-term medical therapies are essential for individuals with recurrence, and should not cease until the tumor is re-localized.

i. Conventional treatment

Conventional medical treatment is mainly composed of phosphate

supplements and active vitamin D preparations (e.g. alfacalcidol and calcitriol) [289]. Conventional medical treatment aims to restore phosphate and vitamin D homeostasis, alleviate the symptoms (weakness, bone pain) and normalize bone mineralization, in order to prevent further deterioration in mobility and bone fractures [1, 265]. It should be recognized that the complete normalization of serum phosphate usually represents an overdose treatment, which may increase the risk of secondary and eventually tertiary hyperparathyroidism [265], and the serum phosphate level has better to barely reach the lower limit of the normal range.

There is a scarcity of information from randomized controlled or prospective research on the optimal dosage of phosphate supplements and active vitamin D preparations. The most recent consensus on the clinical management of TIO recommend a dose of 20-40 mg/kg/d (1-3 g/d for adults) for element phosphate divided into 4-6 doses, and 20-30 ng/kg/d (0.5-1.5μg/d for adults) for calcitriol [265]. The equivalent dosage of alfacalcidol is 1.5 to 2 times that of calcitriol. The dose of medical treatment needs to be adjusted according to the clinical symptoms and biochemical examination results [1, 94, 97]. Several researchers have advocated the use of a vitamin D analogue (e.g. 1alpha-hydroxyvitamin D_3 i.e. alfacalcidol) alone in clinical practice. Peacock and colleagues [290] conducted a study on ten patients with hypophosphatemic osteomalacia, and the results showed that a high dosage of 1alpha-

hydroxyvitamin D_3 without additional phosphate supplements could relieve symptoms rapidly. However, more studies are still needed to determine whether active vitamin D therapy alone could be employed in clinical practice, especially in severe cases of TIO with quite low levels of serum phosphate.

It is important to note that conventional medical therapy may lead to several complications including nephrolithiasis, nephrocalcinosis, impaired kidney function, secondary and even tertiary hyperparathyroidism [93, 218, 291]. The mechanisms underlying the emergence of hyperparathyroidism appear to be multifaceted. In addition to the natural response to the lowering of $1,25(OH)_2D_3$ caused by increased levels of FGF23 [292], long-term use of phosphate supplements can result in subsequent parathyroid gland hyperplasia [1, 293]. In a cross-sectional study of patients with X-linked hypophosphatemia, 10 % of the patients developed hypercalcemic hyperparathyroidism with the treatment of oral phosphate supplements and active vitamin D for more than 10 years [293].

Though higher doses of active vitamin D could help to decrease the elevated level of PTH preventing secondary/tertiary hyperparathyroidism, it increases the risk of hypercalciuria leading to nephrolithiasis and nephrocalcinosis in the mean while. Urine calcium concentration should be measured during the follow-up [294]. Therefore, both the biochemical indicators and imaging performances need to be closely monitored every 3 to 6 months

to balance the optimal clinical improvement and limited treatment complications [265, 294].

ii. Cinacalcet

Cinacalcet, a positive allosteric modulator (PAM) of the calcium-sensing receptor, has been advocated as an adjuvant treatment for patient intolerant of phosphate supplementation [295]. The net effect of cinacalcet treatment was a remarkable increase in serum phosphate level and decrease in PTH level, thereby reducing the dose of phosphate supplements. In a clinical study, the administration of cinacalcet to TIO patients led to a sustained increase in phosphate level and TRP while decreasing serum PTH and calcium levels. The resultant low PTH level was associated with an apparently weakened phosphaturic impact of FGF23, as FGF23 function was found to be partly mediated by PTH [295]. However, cinacalcet doesn't directly annihilate the tumor tissues, and cinacalcet-related hypercalciuria developed frequently. Furthermore, lowering PTH escalates already compromised 1α-hydroxylase activity. Owing to the scarce and inconsistent evidence on cinacalcet [186, 283, 296], additional studies are needed to confirm the efficacy and safety of cinacalcet which has restricted its application in many countries based on the grounds of cost and indication.

iii. Somatostatin

The culprit tumors of TIO are reported to overexpress SSTR, mainly subtype 2, and, therefore, some centers advocate use of somatostatin analogues (SSAs) for the therapy in TIO patients. However, the efficacy of SSA therapy is controversial. The present literature are mostly case reports or case series. Seufert *et a*l [297] reported a 50-year-old patient with TIO was treated with octreotide injections for the first time, and the phosphate level was normalized impressively. While in another case series of 5 TIO patients, there were no significant changes in serum FGF23, $1,25(OH)_2D_3$, or TRP during the 3 days of octreotide treatment [298]. Thus, although SSTRs are widely present in PMTs, octreotide is not an effective therapy to suppress FGF23 production in TIO based on existing works. Inadequate expressions of SSTRs by the culprit tumors and different pathogenic types may partly explain the unsatisfied outcomes.

c. Novel therapies in development or under investigation

i. FGF23 Antibodies

Burosumab (KRN23) is a fully human monoclonal antibody against FGF23, approved for the treatment of X-linked hypophosphatemia (XLH). It could efficaciously normalize phosphate metabolism, ameliorate bone

deformity, and relieve symptoms in XLH patients, rendering it a promising drug for TIO, another FGF23-excess phosphate-wasting disease. The effects of the anti-FGF23 antibody were examined in a murine model, to address if muscle weakness could improve after its use[193]. Indeed, the depletion of ATP and phosphodiesters, as a consequence of hypohosphatemia, has been considered responsible of muscle weakness. The Authors showed that the inhibition of excess FGF23 through antibodies was able to ameliorate both grip strength and spontaneous movement [193].

In two phase 2 open-label trials for TIO conducted in the United States [299] and Asia [300] respectively, promising results were obtained when assessing the efficacy and safety of burosumab in treating patients with TIO. Patients in both studies were subcutaneously treated with burosumab every 4 weeks at an initial dose of 0.3 mg/kg, which was then titrated according to the serum phosphate level at following visits, to a maximum of 2.0 mg/kg. In 112-144 weeks of use, the mean serum phosphate as well as TmP/GFR level rapidly increased above the lower limit of normal and remained through the study course without additional supplementation of oral phosphate [299, 300]. Bone histomorphometry parameters, including osteoid volume/bone, osteoid thickness, and mineralization lag time, were improved and self-reported pain and fatigue were alleviated [299]. Furthermore, approximately 50 % of fractures/pseudofractures observed by whole-body bone scintigraphy were

completely or partially healed by week 96 [299, 300]. Serious burosumab-related adverse events were reported in neither study. In conclusion, the interim analyses revealed that treating TIO with burosumab was associated with normalization of phosphate homeostasis, restored histomorphometric measures, enhanced fracture/pseudofractures healing, relief of symptoms and long-term safety.

Because of the challenge in diagnosis, localization and surgical resection of the causative tumor and post-surgery recurrence, burosumab was progressively regarded as an alternative medical option. Cases of TIO due to unresectable tumors [301], or undetectable tumors [302], and of multiple recurrences after repeated surgeries [303] have been reported to be successfully treated with burosumab. Notably, burosumab at a dose of 0.3 mg/kg exhibited evident therapeutic effects in the recurrent case [303], while the mean final dose in trials above was 0.7 mg/kg -1.0 mg/kg. The discrepancy of burosumab dose was possibly attributed to baseline serum FGF23 level, which was only 56 pg/ml in this case, not even fulfilling the inclusion criteria of the phase 2 studies above, suggesting a theoretical FGF23-independent dosage effect of burosumab.

The safety of burosumab, especially in relation to progression of the underlying tumor, has been monitored. One patient in each study discontinued treatment owing to tumor progression [299, 300] and the other 5

patients had an adverse event of tumor progression, although most of them had a history of tumor progression before enrollment [299]. Notwithstanding the acceptable safety profiles demonstrated by burosumab in these trials, long-term studies are warranted to elucidate the potential role that burosumab plays in tumor progression. Burosumab has been approved in Japan by the U.S. Food and Drug Administration to treat patients age two and older with tumor-induced osteomalacia. Very recently, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) has recommended that burosumab be approved for the treatment of FGF23-related hypophosphatemia in TIO associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in children and adolescents aged 1 to 17 years and in adults.

ii. FGFR Inhibitors

It was hypothesized that the FGF1-FGFR1 signaling pathway remarkably contributed to the pathogenesis of phosphaturic mesenchymal tumor (PMT), given the prevalent expression of FGFR1 in tumor tissues [80]. The identification of *fibronectin1*(*FN1)-FGFR1* fusion gene leading to an overactivation of the FGFR1 kinase domain [79, 80] further strengthened the hypothesis, and naturally arouse interest in the direct blockade of FGFR to obstruct TIO tumorigenesis.

A pan-FGFR tyrosine kinase inhibitor, BGJ398/infigratinib, which was found able to abrogate robust FGF23 signaling and normalize phosphate metabolism in Hyp and *DMP1-null* mice [304], therefore, was tested in clinical trials (NCT02160041 and NCT03510455) for its efficacy and safety on TIO treatment. Although the overall data has not been published yet, cases of patients enrolled demonstrated appreciable therapeutic effects, but there are safety concerns of BGJ398. A patient with TIO due to an unidentifiable tumor also underwent a distinct decline in FGF23 level by day 8 of BGJ398 [305]. Another TIO patient with extensive metastasis responded dramatically to the initiation of BGJ398 treatment, as the FGF23 level dropped to nearly 1/10 of baseline level within 24 hours and became normal after 2 weeks [306]. Metastatic lesions regressed on ^{18}F-FDG-PET-CT scans, and biopsies of one mass showed that the sarcomatous tumor had differentiated into mature lamellar bone. The second round of BGJ398 treatment achieved similar outcomes, including confirmed partial response, normalization of FGF23 and phosphorus levels and tumor differentiation and osseous metaplasia [305]. However, it is noteworthy that BGJ398 treatment in this case was compelled to cease after 18 months because of tyrosine kinase inhibitor-related side effects, despite dose adjustments. The clinical trial (NCT03510455), which planned to enroll 10 patients, terminated the recruitment prematurely, because of a greater than expected incidence of ocular adverse events (AEs) and analysis of the data from the first 4 subjects

indicated that the likelihood of permanent remission with BGJ398 was low. In spite of promising therapeutic implications evidenced by sporadic cases, the clinical practice would probably be limited by its unspecific toxicity, such as stomatitis, diarrhea, anemia, fatigue, renal and liver dysfunction, corneal ulcer and serious retinopathy [305]. The second generation of pan-FGFR inhibitor drugs with higher specificity or FGFR1-specific inhibitors may be prospective solutions worth development and expectation.

d) Other Treatments

Ablative therapy is another treatment option for TIO patients with tumors of which complete resection is challenging due to inaccessible anatomical location, threat to vital nearby structures, or severe comorbidities. It destroys individual tumors with heat (microwave, ultrasound, radiofrequency, or laser ablation), cold (cryoablation), or chemicals (percutaneous ethanol instillation), less traumatically than surgeries, and has certain strengths in the management of soft tissues. Hesse et al innovatively used radiofrequency ablation for TIO and achieved success based on the 1-year follow-up results [307]. Since then, 19 cases in which TIO was treated with ablation have been successively reported [307-316], and among them radiofrequency ablation and cryoablation are predominant with only one exception adopting the ethanol-

cryoablation combination [316]. This technique relies on the guidance of one or multimodality imaging, such as ultrasound and CT augmented by fusion of MRI, ^{18}FDG-PET/CT or ^{68}Ga-DOTATATE PET/CT. The strategy depends upon which modality best defines the tumor margins. Many considerations, including the size and vascularity of the tumor, local resource availability, and other factors, would influence the procedure or combination of procedures to use in a given case. Most cases achieved biochemical restoration and physical improvement. While in the exceptional one large size (5.6×6.5cm) and irregular margins and loculations were proposed to account for the incomplete remission despite increased sessions of radiofrequency ablation [313]. The follow-up times are all shorter than 2 years, far from enough to assess the long-term efficacy of ablative therapy, and case-control studies or cohort studies are in deficiency to provide higher grade evidence on its efficacy and safety.

Peptide receptor radionuclide therapy (PPRT) is an established therapy for neuroendocrine tumors with high somatostatin receptor (SSR) expression [317]. After the somatostatin analog, a component of PPRT, binding to its receptor on the surface of tumor cells, the peptides are internalized and the degradation products in lysosomes mediate radioactivity-induced local damage [317]. Since a proportion of PMTs also expresses SSR, PPRT has a potential therapeutic effect on TIO tumors showing Krenning III/V uptake on

^{68}Ga-DOTATE PET/CT, a recommended sensitive modality to select patients for PRRT [317, 318]. PRRT has been used for repeatedly in patients with TIO due to recurrent cranial tumors [317, 318], and a patient with rare malignant PMT [277]. After 1-4 cycles, the uptake level on ^{68}Ga- DOTATE PET/CT declined, indicating a partial remission in 2/3 cases. Unfortunately, the authors do not report a full time-course of main biochemical parameters of interest [277, 318].

The role of radiotherapy in the multidisciplinary treatment of TIO is not clarified due to the inconsistency of published cases. Massaccesi et al summarized 4 cases of successful radiotherapy use for TIO, among which partial resections of tumors located in the head region without tumor-free margins are the dominant indications [113, 129, 319, 320], while in some cases radiation failed to obtain favorable responses [321, 322]. Different from other therapies, the effect of radiation therapy is not instant, and it may take years to wean off supplementation of phosphate and calcitriol, therefore longer follow-up time is required to monitor the disease and possible radiation-related complications.

7) Conclusions and Future Prospects

Progress has been made in studying the epidemiology, diagnosis, and management of TIO. Thus, studies of this rare disorder have revealed

important insights about the biology of phosphate homeostasis and identified drugs that can be used for the treatment of this disorder for patient benefit. However, many important questions remain unanswered, and some of these, which represent avenues to explore by future research studies, are detailed below.

a. Epidemiology of TIO

1. The epidemiology of TIO needs to be established, and to facilitate this a specific International Classification of Diseases diagnostic code is required. The incidence and prevalence of TIO, together with its age of occurrence and different genders, needs to be determined at global and regional levels as, these may vary in different populations. Identification of such factors may provide insight into the aetiology of TIO.

2. Well-designed studies exploring the short- and long-term impact of TIO on mortality, in patients having curative surgery versus those without surgery, failed surgery, and/or long-term medical treatment, are required.

3. Studies with high quality of evidence should be designed to further the understanding of the burden of disease of TIO from the patient's perspective, and these should include a combination of outcomes including chronic pain, weakness, skeletal-related manifestations and limitations in mobility.
4. The design of a dedicated HRQoL questionnaire will be required to increase the analytical effectiveness of any given treatment in TIO.
5. International registries and biobanks of tumors and blood samples are required for collaborative investigations aimed at understanding the underlying biological processes that would facilitate pre-clinical and translational studies.

b. Molecular and Pathophysiological aspects

1. The regulation of FGF23 production is complex and not fully understood. Thus, the transcription factors regulating FGF23 expression and the mechanisms involved in its post-translational modification (e.g., cleavage) remain to be fully elucidated.
2. The expression and functions of KLOTHO, FGFR1 and the *FN1-FGFR1/FGF1* fusion gene, in TIO cells and in enhancing FGF23 production require further exploration. Also, the mechanisms that

result in FGF23 overproduction in those ~50% of PMTs causing TIO, that do not express the *FN1-FGFR1/FGF1* fusion gene or KLOTHO, need to be characterised.

3. The presence of other “phosphatonins” occurring in patients with typical PMT and osteomalacia, but normal serum FGF23 concentrations, and/or PMTs negative for FGF23 expression, requires study.
4. The roles of *PHEX* and *DMP1* mutations, which are associated with increased FGF23 concentrations, remain to be defined. PHEX, a peptidase expressed in bone, does not cleave FGF23, and PHEX and DMP1 need to interact to lower total plasma FGF23. In addition, the physiological interactions between these local factors and systemic factors (e.g., PTH, 1,25$(OH)_2$D, erythropoietin, iron and alcohol), that regulate FGF23 production, and the pathophysiological consequences stemming from the *PHEX* and *DMP1* mutations need to be fully elucidated.
5. Metabolomic studies in patients with TIO, have revealed potential roles for the oxylipins pathway and TIO pathogenesis. However, these findings need to be confirmed and the effects of confounding factors such as postoperative inflammation, excluded. These represent

important studies as they may potentially identify new targets for therapy.

6. The report that the CaSR likely acts as a phosphate sensor in the parathyroid glands to mediate the stimulatory effect of phosphate on PTH secretion, opens a new target for drugs. Indeed, cinacalcet treatment in TIO patients has been shown to result in a sustained increase in phosphate levels and TRP while decreasing serum PTH and calcium levels. However, cinacalcet may be associated with gastrointestinal side effects in some patients, and trials with other PAMs could be proposed.
7. A search for other phosphate sensors may help to identify novel homeostatic mechanisms and targets for drugs.
8. Some tumors associated with TIO express SSTR2, and it would be important for diagnostic and therapeutic uses to assess expression of other SSTRs (SSTR1, 3, 4 and 5).

c. Imaging techniques for Tumor Localization

1. Current imaging modalities to localize the tumor include a total body nuclear medicine study [e.g., radio-labelled scans (e.g., octreoscans or DOTA scans), SPECT, SPECT-CT, PET, PET-CT] with MRI (or CT) scans,

and these may need to be repeated many times over several years, as the tumors can be very small. However, tumor localization is of paramount importance for facilitating a successful surgical outcome and better imaging modalities are required.

2. Seven Tesla (7T) MRI scanners yield higher resolution images than 3T MRI scanners, which are routinely used in clinical imaging. Thus, 7T MRI scanners are able to provide much more detail and to detect smaller structures. Thus, 7T MRI scanners may be ideally suited for earlier detection of smaller tumors in patients with TIO, and their utility for this purpose needs to be assessed.
3. Octreotide, binds with high affinity to the SSTR2, and PMTs expressing SSTR2 and can be detected by an octreotide scan. However, it is possible that some PMTs may express other SSTRs and targeting these may be of potential use. For example, Pasireotide is a multiple-receptor-targeted SSA that acts via SSTR1, 2, 3, and 5, and generating ^{111}In or ^{68}Ga – labelled pasireotide may be of possible use in detecting some PMTs.
4. Owing to peculiar characteristics of burosumab and assuming that could be labelled with 99Tc, it could potentially be used as a specific diagnostic tool to localise the tumour. Furthermore, if a dose of labelled burosumab were administered pre- or per-operative, it could

be used to help the surgeon identify the precise location of the tumour with the aid of a hand-held gamma camera.

d. Medical treatments in TIO patients with undetectable, inoperable or metastatic tumours

1. Treatment with the FGFR1-3 tyrosine kinase inhibitor, BGJ398/infigratinib, in TIO, resulted in marked biochemical and structural improvements, but was associated with multiple AEs. Hence, the use of second generation of pan-FGFR inhibitor drugs with higher specificity or FGFR1-specific inhibitors require development and evaluation for the treatment of TIO.

2. Burosumab (KRN23), a human monoclonal antibody against FGF23, is reported to be effective in ameliorating the metabolic and skeletal abnormalities of TIO in patients, although tumor progression was observed in some patients. However, long-term studies are required to assess the consequences of such tumor progression in relation to burosumab treatment in TIO, as well as the development and evaluation of other human monoclonal antibodies against FGF23. On a theoretical basis, if busosunmab could be linked to a suitable cytotoxic agent (chemical or radiotherapeutic), it could potentially be used as a therapeutic agent against tumours that are either inoperable because this would involve unacceptable damage to surrounding tissue, or if the tumour is recurrent or if multiple.

3. Effectiveness of multiple-receptor-targeted SSAs, e.g., pasireotide, in treating tumors that express different types of SSTRs needs to be evaluated.

4. Effectiveness of PRRT, which is an established therapy for treating neuroendocrine tumors, for treating PMTs with high SSTR expression, needs to be evaluated.

5. Long follow-up periods will be required to monitor the effectiveness of radiation therapy and possible radiation-related complications.

Acknowledgments

We are thankful to our patients that we had the fortune of managing and treating. This allows us a better approach of future patients.

References:

1. Minisola S, Peacock M, Fukumoto S, et al. Tumour-induced osteomalacia. *Nat Rev Dis Primers*. Jul 13 2017;3:17044. doi:10.1038/nrdp.2017.44
2. Endo I, Fukumoto S, Ozono K, et al. Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment. *Endocr J*. 2015;62(9):811-6. doi:10.1507/endocrj.EJ15-0275
3. Abrahamsen B, Smith CD, Minisola S. Epidemiology of Tumor-Induced Osteomalacia in Denmark. *Calcif Tissue Int*. Aug 2021;109(2):147-156. doi:10.1007/s00223-021-00843-2
4. Rendina D, Abate V, Cacace G, et al. Tumor induced osteomalacia: a systematic review and individual patient's data analysis. *J Clin Endocrinol Metab*. Apr 25 2022;doi:10.1210/clinem/dgac253
5. Crossen SS, Zambrano E, Newman B, et al. Tumor-induced Osteomalacia in a 3-Year-Old With Unresectable Central Giant Cell Lesions. *J Pediatr Hematol Oncol*. Jan 2017;39(1):e21-e24. doi:10.1097/MPH.0000000000000686
6. Jerkovich F, Nunez S, Mocarbel Y, et al. Burden of Disease in Patients With Tumor-Induced Osteomalacia. *JBMR Plus*. Feb 2021;5(2):e10436. doi:10.1002/jbm4.10436
7. Lo SH, Lachmann R, Williams A, Piglowska N, Lloyd AJ. Exploring the burden of X-linked hypophosphatemia: a European multi-country qualitative study. *Qual Life Res*. Jul 2020;29(7):1883-1893. doi:10.1007/s11136-020-02465-x
8. Minisola S, Barlassina A, Vincent SA, Wood S, Williams A. A literature review to understand the burden of disease in people living with tumour-induced osteomalacia. *Osteoporos Int*. May 28 2022;doi:10.1007/s00198-022-06432-9
9. Landis WJ, Jacquet R. Association of calcium and phosphate ions with collagen in the mineralization of vertebrate tissues. *Calcified Tissue International*. Oct 2013;93(4):329-37. doi:10.1007/s00223-013-9725-7
10. Kinoshita Y, Fukumoto S. X-Linked Hypophosphatemia and FGF23-Related Hypophosphatemic Diseases: Prospect for New Treatment. *Endocr Rev*. Jun 1 2018;39(3):274-291. doi:10.1210/er.2017-00220
11. Forster IC, Hernando N, Biber J, Murer H. Phosphate transporters of the SLC20 and SLC34 families. *Mol Aspects Med*. Apr-Jun 2013;34(2-3):386-95. doi:10.1016/j.mam.2012.07.007
12. Peacock M. Phosphate Metabolism in Health and Disease. *Calcified Tissue International*. Jan 2021;108(1):3-15. doi:10.1007/s00223-020-00686-3
13. Segawa H, Yamanaka S, Onitsuka A, et al. Parathyroid hormone-dependent endocytosis of renal type IIc Na-Pi cotransporter. *American journal of physiology Renal physiology*. Jan 2007;292(1):F395-403. doi:10.1152/ajprenal.00100.2006
14. Levi M, Gratton E, Forster IC, et al. Mechanisms of phosphate transport. *Nature reviews Nephrology*. Aug 2019;15(8):482-500. doi:10.1038/s41581-019-0159-y
15. Küng CJ, Haykir B, Schnitzbauer U, Egli-Spichtig D, Hernando N, Wagner CA. Fibroblast growth factor 23 leads to endolysosomal routing of the renal phosphate cotransporters NaPi-IIa and NaPi-IIc in vivo. *American journal of physiology Renal physiology*. Dec 1 2021;321(6):F785-f798. doi:10.1152/ajprenal.00250.2021
16. Portale AA, Zhang MY, David V, et al. Characterization of FGF23-Dependent Egr-1 Cistrome in the

Mouse Renal Proximal Tubule. *PloS one*. 2015;10(11):e0142924. doi:10.1371/journal.pone.0142924

17. Consortium A. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nature Genetics*. Nov 2000;26(3):345-8. doi:10.1038/81664

18. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A*. May 22 2001;98(11):6500-5. doi:10.1073/pnas.101545198

19. Al Rifai O, Susan-Resiga D, Essalmani R, Creemers JWM, Seidah NG, Ferron M. In Vivo Analysis of the Contribution of Proprotein Convertases to the Processing of FGF23. *Frontiers in Endocrinology*. 2021;12:690681. doi:10.3389/fendo.2021.690681

20. Shimada T, Muto T, Urakawa I, et al. Mutant FGF-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. *Endocrinology*. Aug 2002;143(8):3179-82. doi:10.1210/endo.143.8.8795

21. Frishberg Y, Ito N, Rinat C, et al. Hyperostosis-hyperphosphatemia syndrome: a congenital disorder of O-glycosylation associated with augmented processing of fibroblast growth factor 23. *J Bone Miner Res*. Feb 2007;22(2):235-42. doi:10.1359/jbmr.061105

22. Kato K, Jeanneau C, Tarp MA, et al. Polypeptide GalNAc-transferase T3 and familial tumoral calcinosis. Secretion of fibroblast growth factor 23 requires O-glycosylation. *The Journal of Biological Chemistry*. Jul 7 2006;281(27):18370-7. doi:10.1074/jbc.M602469200

23. Tagliabracci VS, Engel JL, Wiley SE, et al. Dynamic regulation of FGF23 by Fam20C phosphorylation, GalNAc-T3 glycosylation, and furin proteolysis. *Proceedings of the National Academy of Sciences of the United States of America*. Apr 15 2014;111(15):5520-5. doi:10.1073/pnas.1402218111

24. Liu S, Guo R, Simpson LG, Xiao ZS, Burnham CE, Quarles LD. Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. *The Journal of Biological Chemistry*. Sep 26 2003;278(39):37419-26. doi:10.1074/jbc.M304544200

25. Fukumoto S, Martin TJ. Bone as an endocrine organ. *Trends Endocrinol Metab*. Jul 2009;20(5):230-6. doi:10.1016/j.tem.2009.02.001

26. Riminucci M, Collins MT, Fedarko NS, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. *J Clin Invest*. Sep 2003;112(5):683-92. doi:10.1172/JCI18399

27. Zofkova I. Involvement of bone in systemic endocrine regulation. *Physiol Res*. Nov 14 2018;67(5):669-677. doi:10.33549/physiolres.933843

28. De Beur SM, Finnegan RB, Vassiliadis J, et al. Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism. *J Bone Miner Res*. Jun 2002;17(6):1102-10. doi:10.1359/jbmr.2002.17.6.1102

29. Goetz R, Beenken A, Ibrahimi OA, et al. Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. *Molecular and cellular biology*. May 2007;27(9):3417-28. doi:10.1128/mcb.02249-06

30. Kurosu H, Ogawa Y, Miyoshi M, et al. Regulation of fibroblast growth factor-23 signaling by klotho. *The Journal of Biological Chemistry*. Mar 10 2006;281(10):6120-3. doi:10.1074/jbc.C500457200

31. Urakawa I, Yamazaki Y, Shimada T, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. Dec 7 2006;444(7120):770-4. doi:10.1038/nature05315

32. Chen G, Liu Y, Goetz R, et al. alpha-Klotho is a non-enzymatic molecular scaffold for FGF23 hormone signalling. *Nature*. Jan 25 2018;553(7689):461-466. doi:10.1038/nature25451

33. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res*. Mar 2004;19(3):429-35. doi:10.1359/JBMR.0301264

34. Shimada T, Kakitani M, Yamazaki Y, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *The Journal of Clinical Investigation*. Feb 2004;113(4):561-8. doi:10.1172/jci19081

35. Sitara D, Razzaque MS, Hesse M, et al. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in Phex-deficient mice. *Matrix Biol*. Nov 2004;23(7):421-32. doi:10.1016/j.matbio.2004.09.007

36. Kolek OI, Hines ER, Jones MD, et al. 1alpha,25-Dihydroxyvitamin D3 upregulates FGF23 gene expression in bone: the final link in a renal-gastrointestinal-skeletal axis that controls phosphate transport. *American journal of physiology Gastrointestinal and liver physiology*. Dec 2005;289(6):G1036-42. doi:10.1152/ajpgi.00243.2005

37. Saito H, Maeda A, Ohtomo S, et al. Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and phosphorus in vivo. *The Journal of Biological Chemistry*. Jan 28 2005;280(4):2543-9. doi:10.1074/jbc.M408903200

38. Lee SM, Carlson AH, Onal M, Benkusky NA, Meyer MB, Pike JW. A Control Region Near the Fibroblast Growth Factor 23 Gene Mediates Response to Phosphate, 1,25(OH)2D3, and LPS In Vivo. *Endocrinology*. Dec 1 2019;160(12):2877-2891. doi:10.1210/en.2019-00622

39. Antoniucci DM, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. *The Journal of Clinical Endocrinology and Metabolism*. Aug 2006;91(8):3144-9. doi:10.1210/jc.2006-0021

40. Ferrari SL, Bonjour JP, Rizzoli R. Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. *The Journal of Clinical Endocrinology and Metabolism*. Mar 2005;90(3):1519-24. doi:10.1210/jc.2004-1039

41. Perwad F, Azam N, Zhang MY, Yamashita T, Tenenhouse HS, Portale AA. Dietary and serum phosphorus regulate fibroblast growth factor 23 expression and 1,25-dihydroxyvitamin D metabolism in mice. *Endocrinology*. Dec 2005;146(12):5358-64. doi:10.1210/en.2005-0777

42. Brown EM, Gamba G, Riccardi D, et al. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. *Nature*. Dec 9 1993;366(6455):575-80. doi:10.1038/366575a0

43. Centeno PP, Herberger A, Mun HC, et al. Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion. *Nat Commun*. Oct 16 2019;10(1):4693. doi:10.1038/s41467-019-12399-9

44. Beck GR, Jr., Knecht N. Osteopontin regulation by inorganic phosphate is ERK1/2-, protein kinase C-, and proteasome-dependent. *The Journal of Biological Chemistry*. Oct 24 2003;278(43):41921-9. doi:10.1074/jbc.M304470200

45. Yamazaki M, Ozono K, Okada T, et al. Both FGF23 and extracellular phosphate activate Raf/MEK/ERK pathway via FGF receptors in HEK293 cells. *Journal of cellular biochemistry*. Dec 1 2010;111(5):1210-21. doi:10.1002/jcb.22842

46. Nishino J, Yamazaki M, Kawai M, et al. Extracellular Phosphate Induces the Expression of Dentin Matrix Protein 1 Through the FGF Receptor in Osteoblasts. *Journal of cellular biochemistry*. May 2017;118(5):1151-1163. doi:10.1002/jcb.25742

47. Takashi Y, Kosako H, Sawatsubashi S, et al. Activation of unliganded FGF receptor by extracellular

phosphate potentiates proteolytic protection of FGF23 by its O-glycosylation. *Proc Natl Acad Sci U S A*. Jun 4 2019;116(23):11418-11427. doi:10.1073/pnas.1815166116

48. Takashi Y, Sawatsubashi S, Endo I, et al. Skeletal FGFR1 signaling is necessary for regulation of serum phosphate level by FGF23 and normal life span. *Biochemistry and biophysics reports*. Sep 2021;27:101107. doi:10.1016/j.bbrep.2021.101107

49. Rhee Y, Bivi N, Farrow E, et al. Parathyroid hormone receptor signaling in osteocytes increases the expression of fibroblast growth factor-23 in vitro and in vivo. *Bone*. Oct 2011;49(4):636-43. doi:10.1016/j.bone.2011.06.025

50. Akiyama KI, Miura Y, Hayashi H, et al. Calciprotein particles regulate fibroblast growth factor-23 expression in osteoblasts. *Kidney International*. Apr 2020;97(4):702-712. doi:10.1016/j.kint.2019.10.019

51. Courbon G, Francis C, Gerber C, et al. Lipocalin 2 stimulates bone fibroblast growth factor 23 production in chronic kidney disease. *Bone research*. Aug 2 2021;9(1):35. doi:10.1038/s41413-021-00154-0

52. Daryadel A, Bettoni C, Haider T, et al. Erythropoietin stimulates fibroblast growth factor 23 (FGF23) in mice and men. *Pflugers Archiv : European journal of physiology*. Oct 2018;470(10):1569-1582. doi:10.1007/s00424-018-2171-7

53. David V, Martin A, Isakova T, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. *Kidney International*. Jan 2016;89(1):135-46. doi:10.1038/ki.2015.290

54. Ewendt F, Feger M, Föller M. Myostatin regulates the production of fibroblast growth factor 23 (FGF23) in UMR106 osteoblast-like cells. *Pflugers Archiv : European journal of physiology*. Jun 2021;473(6):969-976. doi:10.1007/s00424-021-02561-y

55. Ito N, Prideaux M, Wijenayaka AR, et al. Sclerostin Directly Stimulates Osteocyte Synthesis of Fibroblast Growth Factor-23. *Calcified Tissue International*. Jul 2021;109(1):66-76. doi:10.1007/s00223-021-00823-6

56. Ito N, Wijenayaka AR, Prideaux M, et al. Regulation of FGF23 expression in IDG-SW3 osteocytes and human bone by pro-inflammatory stimuli. *Molecular and Cellular Endocrinology*. Jan 5 2015;399:208-18. doi:10.1016/j.mce.2014.10.007

57. Zhang B, Umbach AT, Chen H, et al. Up-regulation of FGF23 release by aldosterone. *Biochemical and Biophysical Research Communications*. Feb 5 2016;470(2):384-390. doi:10.1016/j.bbrc.2016.01.034

58. Bar L, Feger M, Fajol A, et al. Insulin suppresses the production of fibroblast growth factor 23 (FGF23). *Proceedings of the National Academy of Sciences of the United States of America*. May 29 2018;115(22):5804-5809. doi:10.1073/pnas.1800160115

59. Rausch S, Barholz M, Föller M, Feger M. Vitamin A regulates fibroblast growth factor 23 (FGF23). *Nutrition (Burbank, Los Angeles County, Calif)*. Nov-Dec 2020;79-80:110988. doi:10.1016/j.nut.2020.110988

60. Andrukhova O, Slavic S, Odörfer KI, Erben RG. Experimental Myocardial Infarction Upregulates Circulating Fibroblast Growth Factor-23. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. Oct 2015;30(10):1831-9. doi:10.1002/jbmr.2527

61. Bienaimé F, Ambolet A, Aussilhou B, et al. Hepatic Production of Fibroblast Growth Factor 23 in Autosomal Dominant Polycystic Kidney Disease. *The Journal of clinical endocrinology and metabolism*. Jun 1 2018;103(6):2319-2328. doi:10.1210/jc.2018-00123

62. Spichtig D, Zhang H, Mohebbi N, et al. Renal expression of FGF23 and peripheral resistance to elevated FGF23 in rodent models of polycystic kidney disease. *Kidney international*. Jun 2014;85(6):1340-50. doi:10.1038/ki.2013.526

63. van Venrooij NA, Pereira RC, Tintut Y, et al. FGF23 protein expression in coronary arteries is associated with impaired kidney function. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. Aug 2014;29(8):1525-32. doi:10.1093/ndt/gft523

64. Fukumoto S. Phosphate metabolism and vitamin D. *BoneKEy reports*. 2014;3:497. doi:10.1038/bonekey.2013.231

65. Shimada T, Urakawa I, Yamazaki Y, et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. *Biochemical and Biophysical Research Communications*. Feb 6 2004;314(2):409-14. doi:10.1016/j.bbrc.2003.12.102

66. Yamazaki Y, Okazaki R, Shibata M, et al. Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. *J Clin Endocrinol Metab*. Nov 2002;87(11):4957-60. doi:10.1210/jc.2002-021105

67. Boland JM, Tebben PJ, Folpe AL. Phosphaturic mesenchymal tumors: what an endocrinologist should know. *J Endocrinol Invest*. Oct 2018;41(10):1173-1184. doi:10.1007/s40618-018-0849-5

68. Berndt T, Craig TA, Bowe AE, et al. Secreted frizzled-related protein 4 is a potent tumor-derived phosphaturic agent. *J Clin Invest*. Sep 2003;112(5):785-94. doi:10.1172/JCI18563

69. Carpenter TO, Ellis BK, Insogna KL, Philbrick WM, Sterpka J, Shimkets R. Fibroblast growth factor 7: an inhibitor of phosphate transport derived from oncogenic osteomalacia-causing tumors. *J Clin Endocrinol Metab*. Feb 2005;90(2):1012-20. doi:10.1210/jc.2004-0357

70. Rowe PS, Kumagai Y, Gutierrez G, et al. MEPE has the properties of an osteoblastic phosphatonin and minhibin. *Bone*. Feb 2004;34(2):303-19. doi:10.1016/j.bone.2003.10.005

71. Bansal S, Khazim K, Suri R, Martin D, Werner S, Fanti P. Tumor induced osteomalacia: associated with elevated circulating levels of fibroblast growth factor-7 in addition to fibroblast growth factor-23. *Clin Nephrol*. Jan 2016;85(1):57-62. doi:10.5414/CN108596

72. Consortium TH. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. *Nature Genetics*. Oct 1995;11(2):130-6. doi:10.1038/ng1095-130

73. Feng JQ, Ward LM, Liu S, et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. *Nature Genetics*. Nov 2006;38(11):1310-5. doi:10.1038/ng1905

74. Lorenz-Depiereux B, Bastepe M, Benet-Pages A, et al. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. *Nature Genetics*. Nov 2006;38(11):1248-50. doi:10.1038/ng1868

75. Shore RM. Disorders of phosphate homeostasis in children, part 2: hypophosphatemic and hyperphosphatemic disorders. *Pediatr Radiol*. May 10 2022;doi:10.1007/s00247-022-05373-z

76. Beck L, Soumounou Y, Martel J, et al. Pex/PEX tissue distribution and evidence for a deletion in the 3' region of the Pex gene in X-linked hypophosphatemic mice. *The Journal of Clinical Investigation*. Mar 15 1997;99(6):1200-9. doi:10.1172/jci119276

77. Martin A, Liu S, David V, et al. Bone proteins PHEX and DMP1 regulate fibroblastic growth factor Fgf23 expression in osteocytes through a common pathway involving FGF receptor (FGFR) signaling. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. Aug 2011;25(8):2551-62. doi:10.1096/fj.10-177816

78. Xiao Z, Huang J, Cao L, Liang Y, Han X, Quarles LD. Osteocyte-specific deletion of Fgfr1 suppresses FGF23. *PloS One*. 2014;9(8):e104154. doi:10.1371/journal.pone.0104154

79. Lee JC, Jeng YM, Su SY, et al. Identification of a novel FN1-FGFR1 genetic fusion as a frequent event in phosphaturic mesenchymal tumour. *J Pathol*. Mar 2015;235(4):539-45. doi:10.1002/path.4465

80. Lee JC, Su SY, Changou CA, et al. Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors. *Mod Pathol*. Nov 2016;29(11):1335-1346. doi:10.1038/modpathol.2016.137

81. Kinoshita Y, Takashi Y, Ito N, et al. Ectopic expression of Klotho in fibroblast growth factor 23 (FGF23)-producing tumors that cause tumor-induced rickets/osteomalacia (TIO). *Bone Reports*. Jun 2019;10:100192. doi:10.1016/j.bonr.2018.100192

82. Lee CH, Su SY, Sittampalam K, et al. Frequent overexpression of klotho in fusion-negative phosphaturic mesenchymal tumors with tumorigenic implications. *Modern Pathology*. May 2020;33(5):858-870. doi:10.1038/s41379-019-0416-4

83. Moore DD. Physiology. Sister act. *Science (New York, NY)*. Jun 8 2007;316(5830):1436-8. doi:10.1126/science.1144837

84. Roskoski R, Jr. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. *Pharmacological research*. Jan 2020;151:104567. doi:10.1016/j.phrs.2019.104567

85. Prader A, Illig R, Uehlinger E, Stalder G. [Rickets following bone tumor]. *Helv Paediatr Acta*. Dec 1959;14:554-65.

86. Sundaram M, McCarthy EF. Oncogenic osteomalacia. *Skeletal Radiol*. Mar 2000;29(3):117-24. doi:10.1007/s002560050581

87. Folpe AL, Fanburg-Smith JC, Billings SD, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol*. Jan 2004;28(1):1-30. doi:10.1097/00000478-200401000-00001

88. Folpe AL. Phosphaturic mesenchymal tumors: A review and update. *Semin Diagn Pathol*. Jul 2019;36(4):260-268. doi:10.1053/j.semdp.2019.07.002

89. Evans DJ, Azzopardi JG. Distinctive tumours of bone and soft tissue causing acquired vitamin-D-resistant osteomalacia. *Lancet*. Feb 12 1972;1(7746):353-4.

90. Olefsky J, Kempson R, Jones H, Reaven G. "Tertiary" hyperparathyroidism and apparent "cure" of vitamin-D-resistant rickets after removal of an ossifying mesenchymal tumor of the pharynx. *N Engl J Med*. Apr 6 1972;286(14):740-5. doi:10.1056/NEJM197204062861402

91. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. *Cancer*. Apr 15 1987;59(8):1442-54.

92. Folpe AL. Phosphaturic mesenchymal tumour. *Lyon, France: IARC Press*. 2013:211-212.

93. Jiang Y, Xia WB, Xing XP, et al. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: Report of 39 cases and review of the literature. *J Bone Miner Res*. Sep 2012;27(9):1967-75. doi:10.1002/jbmr.1642

94. Yin Z, Du J, Yu F, Xia W. Tumor-induced osteomalacia. *Osteoporos Sarcopenia*. Dec 2018;4(4):119-127. doi:10.1016/j.afos.2018.12.001

95. Li X, Jiang Y, Huo L, et al. Nonremission and Recurrent Tumor-Induced Osteomalacia: A Retrospective Study. *J Bone Miner Res*. Mar 2020;35(3):469-477. doi:10.1002/jbmr.3903

96. Chatterjee D, Bardia A, Pal R, Saikia UN, Bhadada SK, Radotra BD. Clinical, morphological and immunohistochemical analysis of 13 cases of phosphaturic mesenchymal tumor - A holistic diagnostic approach.

Ann Diagn Pathol. Oct 2021;54:151783. doi:10.1016/j.anndiagpath.2021.151783

97. Florenzano P, Hartley IR, Jimenez M, Roszko K, Gafni RI, Collins MT. Tumor-Induced Osteomalacia. *Calcif Tissue Int*. Jan 2021;108(1):128-142. doi:10.1007/s00223-020-00691-6

98. Mishra D, Kaur H, Bhalla AS, et al. Ameloblastic Fibroodontoma of Mandible Causing Tumor Induced Osteomalacia: A Case Report with Review of 88 Phosphaturic Oral Neoplasms. *Head Neck Pathol*. Sep 2021;15(3):975-988. doi:10.1007/s12105-020-01267-4

99. Qari H, Hamao-Sakamoto A, Fuselier C, Cheng YS, Kessler H, Wright J. Phosphaturic Mesenchymal Tumor: 2 New Oral Cases and Review of 53 Cases in the Head and Neck. *Head Neck Pathol*. Jun 2016;10(2):192-200. doi:10.1007/s12105-015-0668-3

100. Wasserman JK, Purgina B, Lai CK, et al. Phosphaturic Mesenchymal Tumor Involving the Head and Neck: A Report of Five Cases with FGFR1 Fluorescence In Situ Hybridization Analysis. *Head Neck Pathol*. Sep 2016;10(3):279-85. doi:10.1007/s12105-015-0678-1

101. Kane SV, Kakkar A, Oza N, Sridhar E, Pai PS. Phosphaturic mesenchymal tumor of the nasal cavity and paranasal sinuses: A clinical curiosity presenting a diagnostic challenge. *Auris Nasus Larynx*. Apr 2018;45(2):377-383. doi:10.1016/j.anl.2017.05.006

102. Villepelet A, Casiraghi O, Temam S, Moya-Plana A. Ethmoid tumor and oncogenic osteomalacia: Case report and review of the literature. *Eur Ann Otorhinolaryngol Head Neck Dis*. Oct 2018;135(5):365-369. doi:10.1016/j.anorl.2018.07.001

103. Wu H, Bui MM, Zhou L, Li D, Zhang H, Zhong D. Phosphaturic mesenchymal tumor with an admixture of epithelial and mesenchymal elements in the jaws: clinicopathological and immunohistochemical analysis of 22 cases with literature review. *Mod Pathol*. Feb 2019;32(2):189-204. doi:10.1038/s41379-018-0100-0

104. Riminucci M CL, Ungari C, Cassoni A, Minisola S, Corsi A. Naso-ethmoidal Mesenchymal Phosphaturic Tumor. A rare tumor site for an uncommon paraneoplastic syndrome. . Ear Nose Throat J 2020.

105. Florenzano P, Gafni RI, Collins MT. Tumor-induced osteomalacia. *Bone Rep*. Dec 2017;7:90-97. doi:10.1016/j.bonr.2017.09.002

106. D'Aguanno V, Ralli M, De Vincentiis L, et al. Sinonasal Angioleiomyoma With Adipocyte Differentiation: Clinicopathologic Study of 2 Cases and Review of the Literature. *Ear Nose Throat J*. Sep 29 2019:145561319878302. doi:10.1177/0145561319878302

107. Li D, Zhu R, Zhou L, Zhong D. Clinical, histopathologic, subtype, and immunohistochemical analysis of jaw phosphaturic mesenchymal tumors. *Medicine (Baltimore)*. Feb 2020;99(7):e19090. doi:10.1097/MD.0000000000019090

108. Stone MD, Quincey C, Hosking DJ. A neuroendocrine cause of oncogenic osteomalacia. *J Pathol*. Jun 1992;167(2):181-5. doi:10.1002/path.1711670204

109. Larsson T, Zahradnik R, Lavigne J, Ljunggren O, Juppner H, Jonsson KB. Immunohistochemical detection of FGF-23 protein in tumors that cause oncogenic osteomalacia. *Eur J Endocrinol*. Feb 2003;148(2):269-76. doi:10.1530/eje.0.1480269

110. Toyosawa S, Tomita Y, Kishino M, et al. Expression of dentin matrix protein 1 in tumors causing oncogenic osteomalacia. *Mod Pathol*. May 2004;17(5):573-8. doi:10.1038/modpathol.3800084

111. Cheung FM, Ma L, Wu WC, Siu TH, Choi PT, Tai YP. Oncogenic osteomalacia associated with an occult phosphaturic mesenchymal tumour: clinico-radiologico-pathological correlation and ultrastructural studies. *Hong Kong Med J*. Aug 2006;12(4):319-21.

112. Houang M, Clarkson A, Sioson L, et al. Phosphaturic mesenchymal tumors show positive staining for

somatostatin receptor 2A (SSTR2A). *Hum Pathol*. Dec 2013;44(12):2711-8. doi:10.1016/j.humpath.2013.07.016

113. Hautmann AH, Schroeder J, Wild P, et al. Tumor-Induced Osteomalacia: Increased Level of FGF-23 in a Patient with a Phosphaturic Mesenchymal Tumor at the Tibia Expressing Periostin. *Case Rep Endocrinol*. 2014;2014:729387. doi:10.1155/2014/729387

114. Creytens D, Van Dorpe J. DOG1 expression in phosphaturic mesenchymal tumour. *J Clin Pathol*. Jul 19 2016;doi:10.1136/jclinpath-2016-203893

115. Shiba E, Matsuyama A, Shibuya R, et al. Immunohistochemical and molecular detection of the expression of FGF23 in phosphaturic mesenchymal tumors including the non-phosphaturic variant. *Diagn Pathol*. Mar 9 2016;11:26. doi:10.1186/s13000-016-0477-3

116. Agaimy A, Michal M, Chiosea S, et al. Phosphaturic Mesenchymal Tumors: Clinicopathologic, Immunohistochemical and Molecular Analysis of 22 Cases Expanding their Morphologic and Immunophenotypic Spectrum. *Am J Surg Pathol*. Oct 2017;41(10):1371-1380. doi:10.1097/PAS.0000000000000890

117. Colangelo L, Cipriani C, Pepe J, et al. A Challenging Case of Tumor-Induced Osteomalacia: Pathophysiological and Clinical Implications. *Calcif Tissue Int*. Oct 2018;103(4):465-468. doi:10.1007/s00223-018-0429-x

118. Yamada Y, Kinoshita I, Kenichi K, et al. Histopathological and genetic review of phosphaturic mesenchymal tumours, mixed connective tissue variant. *Histopathology*. Feb 2018;72(3):460-471. doi:10.1111/his.13377

119. Sent-Doux KN, Mackinnon C, Lee JC, Folpe AL, Habeeb O. Phosphaturic mesenchymal tumor without osteomalacia: additional confirmation of the "nonphosphaturic" variant, with emphasis on the roles of FGF23 chromogenic in situ hybridization and FN1-FGFR1 fluorescence in situ hybridization. *Hum Pathol*. Oct 2018;80:94-98. doi:10.1016/j.humpath.2018.02.022

120. Sun L, Dehner C, Kenney J, et al. Clinicopathologic and molecular features of six cases of phosphaturic mesenchymal tumor. *Virchows Arch*. Apr 2021;478(4):757-765. doi:10.1007/s00428-020-02963-w

121. Jan de Beur SM, Streeten EA, Civelek AC, et al. Localisation of mesenchymal tumours by somatostatin receptor imaging. *Lancet*. Mar 2 2002;359(9308):761-3. doi:10.1016/s0140-6736(02)07846-7

122. Helgebostad R, Revheim ME, Johnsrud K, Amlie K, Alavi A, Connelly JP. Clinical Applications of Somatostatin Receptor (Agonist) PET Tracers beyond Neuroendocrine Tumors. *Diagnostics (Basel)*. Feb 18 2022;12(2)doi:10.3390/diagnostics12020528

123. Weidner N. Review and update: oncogenic osteomalacia-rickets. *Ultrastruct Pathol*. Jul-Oct 1991;15(4-5):317-33. doi:10.3109/01913129109016242

124. Wilkins GE, Granleese S, Hegele RG, Holden J, Anderson DW, Bondy GP. Oncogenic osteomalacia: evidence for a humoral phosphaturic factor. *J Clin Endocrinol Metab*. May 1995;80(5):1628-34. doi:10.1210/jcem.80.5.7745010

125. Shelekhova KV, Kazakov DV, Hes O, Treska V, Michal M. Phosphaturic mesenchymal tumor (mixed connective tissue variant): a case report with spectral analysis. *Virchows Arch*. Feb 2006;448(2):232-5. doi:10.1007/s00428-005-0149-2

126. Bahrami A, Weiss SW, Montgomery E, et al. RT-PCR analysis for FGF23 using paraffin sections in the diagnosis of phosphaturic mesenchymal tumors with and without known tumor induced osteomalacia. *Am J Surg Pathol*. Sep 2009;33(9):1348-54. doi:10.1097/PAS.0b013e3181aa2311

127. Carter JM, Caron BL, Dogan A, Folpe AL. A novel chromogenic in situ hybridization assay for FGF23 mRNA in phosphaturic mesenchymal tumors. *Am J Surg Pathol*. Jan 2015;39(1):75-83.

2002 doi:10.1097/PAS.0000000000000290
2003 128. Ogose A, Hotta T, Emura I, et al. Recurrent malignant variant of phosphaturic mesenchymal tumor with
2004 oncogenic osteomalacia. *Skeletal Radiol*. Feb 2001;30(2):99-103.
2005 129. Uramoto N, Furukawa M, Yoshizaki T. Malignant phosphaturic mesenchymal tumor, mixed connective
2006 tissue variant of the tongue. *Auris Nasus Larynx*. Feb 2009;36(1):104-5. doi:10.1016/j.anl.2008.01.003
2007 130. Sidell D, Lai C, Bhuta S, Barnes L, Chhetri DK. Malignant phosphaturic mesenchymal tumor of the
2008 larynx. *Laryngoscope*. Sep 2011;121(9):1860-3. doi:10.1002/lary.21916
2009 131. Fatani HA, Sunbuli M, Lai SY, Bell D. Phosphaturic mesenchymal tumor: a report of 6 patients treated
2010 at a single institution and comparison with reported series. *Ann Diagn Pathol*. Aug 2013;17(4):319-21.
2011 doi:10.1016/j.anndiagpath.2012.06.005
2012 132. Uchihashi K, Nishijima-Matsunobu A, Matsuyama A, et al. Phosphaturic mesenchymal tumor,
2013 nonphosphaturic variant, causing fatal pulmonary metastasis. *Hum Pathol*. Nov 2013;44(11):2614-8.
2014 doi:10.1016/j.humpath.2013.04.027
2015 133. Morimoto T, Takenaka S, Hashimoto N, Araki N, Myoui A, Yoshikawa H. Malignant phosphaturic
2016 mesenchymal tumor of the pelvis: A report of two cases. *Oncol Lett*. Jul 2014;8(1):67-71.
2017 doi:10.3892/ol.2014.2081
2018 134. Sahoo J, Balachandran K, Kamalanathan S, et al. Tumor(s) induced osteomalacia--a curious case of
2019 double trouble. *J Clin Endocrinol Metab*. Feb 2014;99(2):395-8. doi:10.1210/jc.2013-3791
2020 135. Higley M, Beckett B, Schmahmann S, Dacey E, Foss E. Locally aggressive and multifocal phosphaturic
2021 mesenchymal tumors: two unusual cases of tumor-induced osteomalacia. *Skeletal Radiol*. Dec 2015;44(12):1825-
2022 31. doi:10.1007/s00256-015-2246-x
2023 136. Annamalai AK, Sampathkumar K, Kane S, et al. Needle(s) in the Haystack-Synchronous Multifocal
2024 Tumor-Induced Osteomalacia. *J Clin Endocrinol Metab*. Feb 2016;101(2):390-3. doi:10.1210/jc.2015-3854
2025 137. Arai R, Onodera T, Terkawi MA, Mitsuhashi T, Kondo E, Iwasaki N. A rare case of multiple
2026 phosphaturic mesenchymal tumors along a tendon sheath inducing osteomalacia. *BMC Musculoskelet Disord*. Feb
2027 13 2017;18(1):79. doi:10.1186/s12891-017-1446-z
2028 138. Qiu S, Cao LL, Qiu Y, et al. Malignant phosphaturic mesenchymal tumor with pulmonary metastasis:
2029 A case report. *Medicine (Baltimore)*. Apr 2017;96(17):e6750. doi:10.1097/MD.0000000000006750
2030 139. Yavropoulou MP, Poulios C, Foroulis C, et al. Distant lung metastases caused by a histologically benign
2031 phosphaturic mesenchymal tumor. *Endocrinol Diabetes Metab Case Rep*. 2018;2018doi:10.1530/edm-18-0023
2032 140. Amblee A, Uy J, Senseng C, Hart P. Tumor-induced osteomalacia with normal systemic fibroblast
2033 growth factor-23 level. *Clin Kidney J*. Apr 2014;7(2):186-9. doi:10.1093/ckj/sfu004
2034 141. Kumar R. New insights into phosphate homeostasis: fibroblast growth factor 23 and frizzled-related
2035 protein-4 are phosphaturic factors derived from tumors associated with osteomalacia. *Curr Opin Nephrol*
2036 *Hypertens*. Sep 2002;11(5):547-53. doi:10.1097/00041552-200209000-00011
2037 142. White KE, Larsson TE, Econs MJ. The roles of specific genes implicated as circulating factors involved
2038 in normal and disordered phosphate homeostasis: frizzled related protein-4, matrix extracellular
2039 phosphoglycoprotein, and fibroblast growth factor 23. *Endocr Rev*. May 2006;27(3):221-41. doi:10.1210/er.2005-
2040 0019
2041 143. Shaikh A, Berndt T, Kumar R. Regulation of phosphate homeostasis by the phosphatonins and other
2042 novel mediators. *Pediatr Nephrol*. Aug 2008;23(8):1203-10. doi:10.1007/s00467-008-0751-z
2043 144. Minisola S, Brandi ML. Phosphate Metabolism. *Calcif Tissue Int*. Jan 2021;108(1):1-2.

2044 doi:10.1007/s00223-020-00727-x
2045 145. Amary F, Perez-Casanova L, Ye H, et al. Synovial chondromatosis and soft tissue chondroma:
2046 extraosseous cartilaginous tumor defined by FN1 gene rearrangement. *Mod Pathol*. Dec 2019;32(12):1762-1771.
2047 doi:10.1038/s41379-019-0315-8
2048 146. McMurtry CT, Godschalk M, Malluche HH, Geng Z, Adler RA. Oncogenic osteomalacia associated
2049 with metastatic prostate carcinoma: case report and review of the literature. *J Am Geriatr Soc*. Sep
2050 1993;41(9):983-5. doi:10.1111/j.1532-5415.1993.tb06765.x
2051 147. Nakahama H, Nakanishi T, Uno H, et al. Prostate cancer-induced oncogenic hypophosphatemic
2052 osteomalacia. *Urol Int*. 1995;55(1):38-40. doi:10.1159/000282746
2053 148. Jing H, Li F, Zhuang H, et al. Effective detection of the tumors causing osteomalacia using [Tc-99m]-
2054 HYNIC-octreotide (99mTc-HYNIC-TOC) whole body scan. *Eur J Radiol*. Nov 2013;82(11):2028-34.
2055 doi:10.1016/j.ejrad.2013.04.006
2056 149. Leaf DE, Pereira RC, Bazari H, Juppner H. Oncogenic osteomalacia due to FGF23-expressing colon
2057 adenocarcinoma. *J Clin Endocrinol Metab*. Mar 2013;98(3):887-91. doi:10.1210/jc.2012-3473
2058 150. Xie Y, Li HZ. Oncogenic osteomalacia caused by renal cell carcinoma. *J Clin Endocrinol Metab*. Dec
2059 2013;98(12):4597-8. doi:10.1210/jc.2013-3335
2060 151. Lin HA, Shih SR, Tseng YT, et al. Ovarian cancer-related hypophosphatemic osteomalacia--a case
2061 report. *J Clin Endocrinol Metab*. Dec 2014;99(12):4403-7. doi:10.1210/jc.2014-2120
2062 152. Abate EG, Bernet V, Cortese C, Garner HW. Tumor induced osteomalacia secondary to anaplastic
2063 thyroid carcinoma: A case report and review of the literature. *Bone Rep*. Dec 2016;5:81-85.
2064 doi:10.1016/j.bonr.2015.11.004
2065 153. Sauder A, Wiernek S, Dai X, et al. FGF23-Associated Tumor-Induced Osteomalacia in a Patient With
2066 Small Cell Carcinoma: A Case Report and Regulatory Mechanism Study. *Int J Surg Pathol*. Apr 2016;24(2):116-
2067 20. doi:10.1177/1066896915617828
2068 154. Savva C, Adhikaree J, Madhusudan S, Chokkalingam K. Oncogenic osteomalacia and metastatic breast
2069 cancer: a case report and review of the literature. *J Diabetes Metab Disord*. Jun 2019;18(1):267-272.
2070 doi:10.1007/s40200-019-00398-y
2071 155. Kelly TG, Shattuck TM, Reyes-Mugica M, et al. Surveillance for early detection of aggressive
2072 parathyroid disease: carcinoma and atypical adenoma in familial isolated hyperparathyroidism associated with a
2073 germline HRPT2 mutation. *J Bone Miner Res*. Oct 2006;21(10):1666-71. doi:10.1359/jbmr.060702
2074 156. Elderman JH, Wabbijn M, de Jongh F. Hypophosphataemia due to FGF-23 producing B cell non-
2075 Hodgkin's lymphoma. *BMJ Case Rep*. Apr 26 2016;2016doi:10.1136/bcr-2015-213954
2076 157. Reinert RB, Bixby D, Koenig RJ. Fibroblast Growth Factor 23-Induced Hypophosphatemia in Acute
2077 Leukemia. *J Endocr Soc*. May 1 2018;2(5):437-443. doi:10.1210/js.2018-00010
2078 158. Haviv YS, Silver J. Late onset oncogenic osteomalacia-associated with neurofibromatosis type II. *Clin*
2079 *Nephrol*. Nov 2000;54(5):429-30.
2080 159. Chadha M, Singh AP, Singh AP. Hypophosphataemic osteomalacia in neurofibromatosis. *Acta Orthop*
2081 *Belg*. Dec 2009;75(6):847-50.
2082 160. Obo T, Koriyama N, Tokito A, Ogiso K, Nishio Y. Neurofibromatosis type 1 associated with
2083 hypophosphatemic osteomalacia due to hypersecretion of fibroblast growth factor 23: a case report. *J Med Case*
2084 *Rep*. May 9 2020;14(1):56. doi:10.1186/s13256-020-02381-1
2085 161. Makhlouf Y, Boussaid S, Ajlani H, et al. A Rare Case of Hypophosphataemic Osteomalacia in von

Recklinghausen Neurofibromatosis. *Eur J Case Rep Intern Med*. 2021;8(5):002618. doi:10.12890/2021_002618

162. Collins MT, Chebli C, Jones J, et al. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. *J Bone Miner Res*. May 2001;16(5):806-13. doi:10.1359/jbmr.2001.16.5.806

163. Yamamoto T, Miyamoto KI, Ozono K, et al. Hypophosphatemic rickets accompanying McCune-Albright syndrome: evidence that a humoral factor causes hypophosphatemia. *J Bone Miner Metab*. 2001;19(5):287-95. doi:10.1007/s007740170012

164. de Castro LF, Ovejero D, Boyce AM. DIAGNOSIS OF ENDOCRINE DISEASE: Mosaic disorders of FGF23 excess: Fibrous dysplasia/McCune-Albright syndrome and cutaneous skeletal hypophosphatemia syndrome. *Eur J Endocrinol*. May 2020;182(5):R83-R99. doi:10.1530/EJE-19-0969

165. Lim YH, Ovejero D, Sugarman JS, et al. Multilineage somatic activating mutations in HRAS and NRAS cause mosaic cutaneous and skeletal lesions, elevated FGF23 and hypophosphatemia. *Hum Mol Genet*. Jan 15 2014;23(2):397-407. doi:10.1093/hmg/ddt429

166. Ovejero D, Lim YH, Boyce AM, et al. Cutaneous skeletal hypophosphatemia syndrome: clinical spectrum, natural history, and treatment. *Osteoporos Int*. Dec 2016;27(12):3615-3626. doi:10.1007/s00198-016-3702-8

167. Park PG, Park E, Hyun HS, et al. Cutaneous Skeletal Hypophosphatemia Syndrome in Association with a Mosaic HRAS Mutation. *Ann Clin Lab Sci*. Sep 2018;48(5):665-669.

168. Lim YH, Ovejero D, Derrick KM, Yale Center for Mendelian G, Collins MT, Choate KA. Cutaneous skeletal hypophosphatemia syndrome (CSHS) is a multilineage somatic mosaic RASopathy. *J Am Acad Dermatol*. Aug 2016;75(2):420-7. doi:10.1016/j.jaad.2015.11.012

169. White KE, Cabral JM, Davis SI, et al. Mutations that cause osteoglophonic dysplasia define novel roles for FGFR1 in bone elongation. *Am J Hum Genet*. Feb 2005;76(2):361-7. doi:10.1086/427956

170. Schouten BJ, Doogue MP, Soule SG, Hunt PJ. Iron polymaltose-induced FGF23 elevation complicated by hypophosphataemic osteomalacia. *Ann Clin Biochem*. Mar 2009;46(Pt 2):167-9. doi:10.1258/acb.2008.008151

171. Shimizu Y, Tada Y, Yamauchi M, et al. Hypophosphatemia induced by intravenous administration of saccharated ferric oxide: another form of FGF23-related hypophosphatemia. *Bone*. Oct 2009;45(4):814-6. doi:10.1016/j.bone.2009.06.017

172. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res*. Aug 2013;28(8):1793-803. doi:10.1002/jbmr.1923

173. Hidaka N, Kato H, Koga M, et al. Induction of FGF23-related hypophosphatemic osteomalacia by alcohol consumption. *Bone Rep*. Dec 2021;15:101144. doi:10.1016/j.bonr.2021.101144

174. Kulak CA, Dempster DW. Bone histomorphometry: a concise review for endocrinologists and clinicians. *Arq Bras Endocrinol Metabol*. Mar 2010;54(2):87-98. doi:10.1590/s0004-27302010000200002

175. Siris ES, Clemens TL, Dempster DW, et al. Tumor-induced osteomalacia. Kinetics of calcium, phosphorus, and vitamin D metabolism and characteristics of bone histomorphometry. *Am J Med*. Feb 1987;82(2):307-12. doi:10.1016/0002-9343(87)90075-1

176. Cai Q, Hodgson SF, Kao PC, et al. Brief report: inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med*. Jun 9 1994;330(23):1645-9. doi:10.1056/NEJM199406093302304

177. Gore MO, Welch BJ, Geng W, et al. Renal phosphate wasting due to tumor-induced osteomalacia: a

frequently delayed diagnosis. *Kidney Int*. Aug 2009;76(3):342-7. doi:10.1038/ki.2008.355

178. Corsi A, Ippolito E, Robey PG, Riminucci M, Boyde A. Bisphosphonate-induced zebra lines in fibrous dysplasia of bone: histo-radiographic correlation in a case of McCune-Albright syndrome. *Skeletal Radiol*. Oct 2017;46(10):1435-1439. doi:10.1007/s00256-017-2698-2

179. Feng J, Jiang Y, Wang O, et al. The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases. *Endocr J*. Jul 28 2017;64(7):675-683. doi:10.1507/endocrj.EJ16-0587

180. Shah R, Lila AR, Jadhav RS, et al. Tumor induced osteomalacia in head and neck region: single center experience and systematic review. *Endocr Connect*. Oct 2019;8(10):1330-1353. doi:10.1530/EC-19-0341

181. Colangelo L, Pepe J, Nieddu L, et al. Long-term bone mineral density changes after surgical cure of patients with tumor-induced osteomalacia. *Osteoporos Int*. Jul 2020;31(7):1383-1387. doi:10.1007/s00198-020-05369-1

182. Zhao Z, Chen W, Wang Y, et al. Comparative Analysis of Clinical and Imaging Features of Osteomalacia and Spondyloarthritis. *Front Med (Lausanne)*. 2021;8:680598. doi:10.3389/fmed.2021.680598

183. Kawthalkar AS, Janu AK, Deshpande MS, Gala KB, Gulia A, Puri A. Phosphaturic Mesenchymal Tumors from Head to Toe: Imaging Findings and Role of the Radiologist in Diagnosing Tumor-Induced Osteomalacia. *Indian J Orthop*. Apr 2020;54(2):215-223. doi:10.1007/s43465-019-00005-5

184. Chang CY, Rosenthal DI, Mitchell DM, Handa A, Kattapuram SV, Huang AJ. Imaging Findings of Metabolic Bone Disease. *Radiographics*. Oct 2016;36(6):1871-1887. doi:10.1148/rg.2016160004

185. Le May M, Blunt JW, Jr. A Factor Determining the Location of Pseudofractures in Osteomalacia. *J Clin Invest*. May 1949;28(3):521-5. doi:10.1172/JCI102099

186. Chong WH, Andreopoulou P, Chen CC, et al. Tumor localization and biochemical response to cure in tumor-induced osteomalacia. *J Bone Miner Res*. Jun 2013;28(6):1386-98. doi:10.1002/jbmr.1881

187. Piemonte S, Romagnoli E, Cipriani C, et al. Six-year follow-up of a characteristic osteolytic lesion in a patient with tumor-induced osteomalacia. *Eur J Endocrinol*. Jan 2014;170(1):K1-4. doi:10.1530/EJE-13-0581

188. Ni X, Feng Y, Guan W, et al. Bone Impairment in a Large Cohort of Chinese Patients With Tumor-Induced Osteomalacia Assessed by HR-pQCT and TBS. *J Bone Miner Res*. Mar 2022;37(3):454-464. doi:10.1002/jbmr.4476

189. Mendes DAB, Coelho MCA, Gehrke B, et al. Microarchitectural parameters and bone mineral density in patients with tumour-induced osteomalacia by HR-pQCT and DXA. *Clin Endocrinol (Oxf)*. Oct 2021;95(4):587-594. doi:10.1111/cen.14533

190. Zanchetta MB, Jerkovich F, Nunez S, et al. Impaired bone microarchitecture and strength in patients with tumor-induced osteomalacia. *J Bone Miner Res*. Aug 2021;36(8):1502-1509. doi:10.1002/jbmr.4325

191. Satyaraddi A, Cherian KE, Shetty S, et al. Musculoskeletal oncogenic osteomalacia-An experience from a single centre in South India. *J Orthop*. Mar 2017;14(1):184-188. doi:10.1016/j.jor.2016.12.010

192. Kumar R, Folpe AL, Mullan BP. Tumor-Induced Osteomalacia. *Transl Endocrinol Metab*. Summer 2015;7(3)

193. Aono Y, Hasegawa H, Yamazaki Y, et al. Anti-FGF-23 neutralizing antibodies ameliorate muscle weakness and decreased spontaneous movement of Hyp mice. *J Bone Miner Res*. Apr 2011;26(4):803-10. doi:10.1002/jbmr.275

194. Baroncelli GI, Mora S. X-Linked Hypophosphatemic Rickets: Multisystemic Disorder in Children Requiring Multidisciplinary Management. *Front Endocrinol (Lausanne)*. 2021;12:688309. doi:10.3389/fendo.2021.688309

195. Brociek-Pilczynska A, Brodowska-Kania D, Szczygielski K, et al. A rare combination of tumor-induced osteomalacia caused by sinonasal glomangiopericytoma and coexisting parathyroid adenoma: case report and literature review. *BMC Endocr Disord*. Jan 28 2022;22(1):31. doi:10.1186/s12902-022-00934-7

196. Huang QL, Feig DS, Blackstein ME. Development of tertiary hyperparathyroidism after phosphate supplementation in oncogenic osteomalacia. *J Endocrinol Invest*. Apr 2000;23(4):263-7. doi:10.1007/BF03343720

197. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest*. Nov 2011;121(11):4393-408. doi:10.1172/JCI46122

198. Takashi Y, Kinoshita Y, Hori M, Ito N, Taguchi M, Fukumoto S. Patients with FGF23-related hypophosphatemic rickets/osteomalacia do not present with left ventricular hypertrophy. *Endocr Res*. May 2017;42(2):132-137. doi:10.1080/07435800.2016.1242604

199. Agrawal K, Padhy BM, Meher BR, Mohanty RR. Diagnostic utility of Ga-68 DOTA-SSTR and F-18 FDG PET/CT in the detection of culprit tumours causing osteomalacia: a systematic review and meta-analysis. *Nucl Med Commun*. Jun 1 2021;42(6):646-655. doi:10.1097/MNM.0000000000001379

200. Crotti C, Bartoli F, Coletto LA, et al. Tumor induced osteomalacia: A single center experience on 17 patients. *Bone*. Nov 2021;152:116077. doi:10.1016/j.bone.2021.116077

201. Gonzalez G, Baudrand R, Sepulveda MF, et al. Tumor-induced osteomalacia: experience from a South American academic center. *Osteoporos Int*. Jul 2017;28(7):2187-2193. doi:10.1007/s00198-017-4007-2

202. Pal R, Bhadada SK, Singhare A, et al. Tumor-induced osteomalacia: experience from three tertiary care centers in India. *Endocr Connect*. Mar 2019;8(3):266-276. doi:10.1530/EC-18-0552

203. Walton RJ, Bijvoet OL. Nomogram for derivation of renal threshold phosphate concentration. *Lancet*. Aug 16 1975;2(7929):309-10. doi:10.1016/s0140-6736(75)92736-1

204. Mc CR. Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. *Q J Med*. Jan 1947;16(1):33-46.

205. El-Maouche D, Sadowski SM, Papadakis GZ, et al. (68)Ga-DOTATATE for Tumor Localization in Tumor-Induced Osteomalacia. *J Clin Endocrinol Metab*. Oct 2016;101(10):3575-3581. doi:10.1210/jc.2016-2052

206. Imel EA, Peacock M, Pitukcheewanont P, et al. Sensitivity of fibroblast growth factor 23 measurements in tumor-induced osteomalacia. *J Clin Endocrinol Metab*. Jun 2006;91(6):2055-61. doi:10.1210/jc.2005-2105

207. Imel EA, Peacock M, Gray AK, Padgett LR, Hui SL, Econs MJ. Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. *J Clin Endocrinol Metab*. Nov 2011;96(11):3541-9. doi:10.1210/jc.2011-1239

208. Smith ER, McMahon LP, Holt SG. Method-specific differences in plasma fibroblast growth factor 23 measurement using four commercial ELISAs. *Clin Chem Lab Med*. Oct 2013;51(10):1971-81. doi:10.1515/cclm-2013-0208

209. Goetz R, Nakada Y, Hu MC, et al. Isolated C-terminal tail of FGF23 alleviates hypophosphatemia by inhibiting FGF23-FGFR-Klotho complex formation. *Proc Natl Acad Sci U S A*. Jan 05 2010;107(1):407-12. doi:10.1073/pnas.0902006107

210. Xia WB, Jiang Y, Li M, et al. Levels and dynamic changes of serum fibroblast growth factor 23 in hypophosphatemic rickets/osteomalacia. *Chin Med J (Engl)*. May 5 2010;123(9):1158-62.

211. Cipriani C MS, Colangelo L, De Martino V, Ferrone F, Biamonte F, Danese V, Sonato C, Santori R, Occhiuto M, Pepe J. FGF23 functions and disease. *Minerva Endocrinol*. 2021;doi:10.23736/S2724-6507.21.03378-2

212. Kato H, Hidaka N, Koga M, et al. Performance evaluation of the new chemiluminescent intact FGF23 assay relative to the existing assay system. *J Bone Miner Metab*. Jan 2022;40(1):101-108. doi:10.1007/s00774-021-01258-7

213. Jonsson KB, Zahradnik R, Larsson T, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med*. Apr 24 2003;348(17):1656-63. doi:10.1056/NEJMoa020881

214. Jadhav S, Kasaliwal R, Lele V, et al. Functional imaging in primary tumour-induced osteomalacia: relative performance of FDG PET/CT vs somatostatin receptor-based functional scans: a series of nine patients. *Clin Endocrinol (Oxf)*. Jul 2014;81(1):31-7. doi:10.1111/cen.12426

215. Honda R, Kawabata Y, Ito S, Kikuchi F. Phosphaturic mesenchymal tumor, mixed connective tissue type, non-phosphaturic variant: report of a case and review of 32 cases from the Japanese published work. *J Dermatol*. Sep 2014;41(9):845-9. doi:10.1111/1346-8138.12602

216. Breer S, Brunkhorst T, Beil FT, et al. 68Ga DOTA-TATE PET/CT allows tumor localization in patients with tumor-induced osteomalacia but negative 111In-octreotide SPECT/CT. *Bone*. Jul 2014;64:222-7. doi:10.1016/j.bone.2014.04.016

217. Agrawal K, Bhadada S, Mittal BR, et al. Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia. *Clin Nucl Med*. Jan 2015;40(1):e6-e10. doi:10.1097/RLU.0000000000000460

218. Yu WJ, He JW, Fu WZ, Wang C, Zhang ZL. Reports of 17 Chinese patients with tumor-induced osteomalacia. *J Bone Miner Metab*. May 2017;35(3):298-307. doi:10.1007/s00774-016-0756-9

219. Nandam N, Ejaz S, Ahrens W, Styner M. A Normal FGF23 Does Not Preclude Tumor-Induced Osteomalacia. *JBMR Plus*. Feb 2021;5(2):e10438. doi:10.1002/jbm4.10438

220. Velazquez-Navarro JA, Loya-Teruel E, Rios-Gomez M, Montes-Ramirez JE. Tumor-Induced Osteomalacia With Normal Fibroblast Growth Factor-23 (FGF23) and Idiopathic Hypercalciuria. *Cureus*. Jan 2022;14(1):e20893. doi:10.7759/cureus.20893

221. Gong Y, Ni X, Jin C, et al. Serum Metabolomics Reveals Dysregulation and Diagnostic Potential of Oxylipins in Tumor-induced Osteomalacia. *J Clin Endocrinol Metab*. Apr 19 2022;107(5):1383-1391. doi:10.1210/clinem/dgab885

222. Marozzi M, Parnigoni A, Negri A, et al. Inflammation, Extracellular Matrix Remodeling, and Proteostasis in Tumor Microenvironment. *Int J Mol Sci*. Jul 28 2021;22(15)doi:10.3390/ijms22158102

223. Gabbs M, Leng S, Devassy JG, Monirujjaman M, Aukema HM. Advances in Our Understanding of Oxylipins Derived from Dietary PUFAs. *Adv Nutr*. Sep 2015;6(5):513-40. doi:10.3945/an.114.007732

224. Moore GY, Pidgeon GP. Cross-Talk between Cancer Cells and the Tumour Microenvironment: The Role of the 5-Lipoxygenase Pathway. *Int J Mol Sci*. Jan 24 2017;18(2)doi:10.3390/ijms18020236

225. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. Dec 19-26 2002;420(6917):860-7. doi:10.1038/nature01322

226. Ding XZ, Iversen P, Cluck MW, Knezetic JA, Adrian TE. Lipoxygenase inhibitors abolish proliferation of human pancreatic cancer cells. *Biochem Biophys Res Commun*. Jul 22 1999;261(1):218-23. doi:10.1006/bbrc.1999.1012

227. Chung JW, Kim GY, Mun YC, Ahn JY, Seong CM, Kim JH. Leukotriene B4 pathway regulates the fate of the hematopoietic stem cells. *Exp Mol Med*. Feb 28 2005;37(1):45-50. doi:10.1038/emm.2005.6

228. Hoque A, Lippman SM, Wu TT, et al. Increased 5-lipoxygenase expression and induction of apoptosis by its inhibitors in esophageal cancer: a potential target for prevention. *Carcinogenesis*. Apr 2005;26(4):785-91.

doi:10.1093/carcin/bgi026

229. Paruchuri S, Mezhybovska M, Juhas M, Sjolander A. Endogenous production of leukotriene D4 mediates autocrine survival and proliferation via CysLT1 receptor signalling in intestinal epithelial cells. *Oncogene*. Oct 26 2006;25(50):6660-5. doi:10.1038/sj.onc.1209666

230. Kim GY, Lee JW, Ryu HC, Wei JD, Seong CM, Kim JH. Proinflammatory cytokine IL-1beta stimulates IL-8 synthesis in mast cells via a leukotriene B4 receptor 2-linked pathway, contributing to angiogenesis. *J Immunol*. Apr 1 2010;184(7):3946-54. doi:10.4049/jimmunol.0901735

231. Kim GY, Lee JW, Cho SH, Seo JM, Kim JH. Role of the low-affinity leukotriene B4 receptor BLT2 in VEGF-induced angiogenesis. *Arterioscler Thromb Vasc Biol*. Jun 2009;29(6):915-20. doi:10.1161/ATVBAHA.109.185793

232. Zhang G, Panigrahy D, Mahakian LM, et al. Epoxy metabolites of docosahexaenoic acid (DHA) inhibit angiogenesis, tumor growth, and metastasis. *Proc Natl Acad Sci U S A*. Apr 16 2013;110(16):6530-5. doi:10.1073/pnas.1304321110

233. Mountziaris PM, Mikos AG. Modulation of the inflammatory response for enhanced bone tissue regeneration. *Tissue Eng Part B Rev*. Jun 2008;14(2):179-86. doi:10.1089/ten.teb.2008.0038

234. Jiang Y, Hou G, Cheng W. Performance of 68Ga-DOTA-SST PET/CT, octreoscan SPECT/CT and 18F-FDG PET/CT in the detection of culprit tumors causing osteomalacia: a meta-analysis. *Nucl Med Commun*. Apr 2020;41(4):370-376. doi:10.1097/MNM.0000000000001163

235. Rayamajhi SJ, Yeh R, Wong T, et al. Tumor-induced osteomalacia - Current imaging modalities and a systematic approach for tumor localization. *Clin Imaging*. Jul - Aug 2019;56:114-123. doi:10.1016/j.clinimag.2019.04.007

236. Zhang J, Zhu Z, Zhong D, et al. 68Ga DOTATATE PET/CT is an Accurate Imaging Modality in the Detection of Culprit Tumors Causing Osteomalacia. *Clin Nucl Med*. Aug 2015;40(8):642-6. doi:10.1097/RLU.0000000000000854

237. Reubi JC, Schar JC, Waser B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med*. Mar 2000;27(3):273-82.

238. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. *Radiographics*. Mar-Apr 2015;35(2):500-16. doi:10.1148/rg.352140164

239. Ding J, Hu G, Wang L, Li F, Huo L. Increased Activity Due to Fractures Does Not Significantly Affect the Accuracy of 68Ga-DOTATATE PET/CT in the Detection of Culprit Tumor in the Evaluation of Tumor-Induced Osteomalacia. *Clin Nucl Med*. Dec 2018;43(12):880-886. doi:10.1097/RLU.0000000000002290

240. Long T, Hou J, Yang N, et al. Utility of 18F-AlF-NOTA-Octreotide PET/CT in the Localization of Tumor-Induced Osteomalacia. *J Clin Endocrinol Metab*. Sep 27 2021;106(10):e4202-e4209. doi:10.1210/clinem/dgab258

241. Jain AS, Shelley S, Muthukrishnan I, Kalal S, Amalachandran J, Chandran S. Diagnostic importance of contrast enhanced (18)F-fluorodeoxyglucose positron emission computed tomography in patients with tumor induced osteomalacia: Our experience. *Indian J Nucl Med*. Jan-Mar 2016;31(1):14-9. doi:10.4103/0972-3919.172344

242. Metser U, Even-Sapir E. Increased (18)F-fluorodeoxyglucose uptake in benign, nonphysiologic lesions found on whole-body positron emission tomography/computed tomography (PET/CT): accumulated data from

2296 four years of experience with PET/CT. *Semin Nucl Med*. May 2007;37(3):206-22.
2297 doi:10.1053/j.semnuclmed.2007.01.001
2298 243. Costelloe CM, Murphy WA, Jr., Chasen BA. Musculoskeletal pitfalls in 18F-FDG PET/CT: pictorial
2299 review. *AJR Am J Roentgenol*. Sep 2009;193(3 Suppl):WS1-WS13, Quiz S26-30. doi:10.2214/AJR.07.7138
2300 244. Wang P, Zhang S, Huo L, Jing H, Li F. Prognostic Value of Positive Presurgical FDG PET/CT in the
2301 Evaluation of Tumor-Induced Osteomalacia. *Clin Nucl Med*. Mar 1 2021;46(3):214-219.
2302 doi:10.1097/RLU.0000000000003463
2303 245. Ferraz MP, Watanabe T, Sado HN, et al. Concordance between whole-body scintigraphy 111In-
2304 octreotide and 99mTc-sestamibi uptake in the detection of four tumor-induced osteomalacia cases. *J Clin*
2305 *Endocrinol Metab*. Mar 2014;99(3):699-700. doi:10.1210/jc.2013-3563
2306 246. Andreopoulou P, Dumitrescu CE, Kelly MH, et al. Selective venous catheterization for the localization
2307 of phosphaturic mesenchymal tumors. *J Bone Miner Res*. Jun 2011;26(6):1295-302. doi:10.1002/jbmr.316
2308 247. Sciubba DM, Petteys RJ, Shakur SF, et al. En bloc spondylectomy for treatment of tumor-induced
2309 osteomalacia. *J Neurosurg Spine*. Nov 2009;11(5):600-4. doi:10.3171/2009.6.SPINE08120
2310 248. Hidaka N KM, Kimura S, Hoshino Y, Kato H, Kinoshita Y, Makita N, Nangaku M, Horiguchi K,
2311 Furukawa Y, Ohnaka K, Inagaki K, Nakagawa A, Suzuki A, Takeuchi Y, Fukumoto S, Nakatani F, Ito N. Clinical
2312 challenges in diagnosis, tumor localization and treatment of tumor-induced
2313 osteomalacia: outcome of a retrospective surveillance. *J Bone Miner Res* 2022;doi:10.1002/jbmr.4620
2314 249. J. Feng YJ, O. Wang, M. Li, X. Xing, L. Huo, F. Li, W. Yu, D.R. Zhong, J. Jin, Y. Liu, F. Qi, W. Lv, L.
2315 Zhou, X.W. Meng, W.B. Xia. The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of
2316 144 cases. *Endocr J*. 2017;64:675-683.
2317 250. Brandi M CG, Houillier P, Jan de Beur d SM, Minisola S, Oheim R, Seefried L. Challenges in the
2318 management of tumor-induced osteomalacia (TIO). *Bone*. 2021;152:116064.
2319 251. Florenzano P, Cipriani C, Roszko KL, et al. Approach to patients with hypophosphataemia. *Lancet*
2320 *Diabetes Endocrinol*. Feb 2020;8(2):163-174. doi:10.1016/S2213-8587(19)30426-7
2321 252. Caio G VU, Sapone A, Leffler DA, De Giorgio R, Catassi C, Fasano A. Celiac disease: a comprehensive
2322 current review. *BMC Medicine*. 2019;17(142)
2323 253. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr Relat Cancer*.
2324 Jun 2011;18(3):R53-77. doi:10.1530/ERC-11-0006
2325 254. Heijboer AC CE. The measurement and interpretation of fibroblast growth factor 23 (FGF23)
2326 concentrations. *Calcified Tissue Int*. 2022;doi:10.1007/s00223-022-00987-9
2327 255. Tafti D CN. Fibrous dysplasia. *StatPearls [Internet]*. StatPearls Publishin LLC; 2022.
2328 256. Corsi A, Cherman N, Donaldson DL, Robey PG, Collins MT, Riminucci M. Neonatal McCune-Albright
2329 Syndrome: A Unique Syndromic Profile With an Unfavorable Outcome. *JBMR Plus*. Aug 2019;3(8):e10134.
2330 doi:10.1002/jbm4.10134
2331 257. Ippolito E, Bray EW, Corsi A, et al. Natural history and treatment of fibrous dysplasia of bone: a
2332 multicenter clinicopathologic study promoted by the European Pediatric Orthopaedic Society. *J Pediatr Orthop*
2333 *B*. May 2003;12(3):155-77. doi:10.1097/01.bpb.0000064021.41829.94
2334 258. Ippolito E, Farsetti P, Boyce AM, Corsi A, De Maio F, Collins MT. Radiographic classification of
2335 coronal plane femoral deformities in polyostotic fibrous dysplasia. *Clin Orthop Relat Res*. May 2014;472(5):1558-
2336 67. doi:10.1007/s11999-013-3380-1
2337 259. Mancini F, Corsi A, De Maio F, Riminucci M, Ippolito E. Scoliosis and spine involvement in fibrous

dysplasia of bone. *Eur Spine J*. Feb 2009;18(2):196-202. doi:10.1007/s00586-008-0860-1

260. Diacinti D CC, Biamonte F, Pepe J, Colangelo L, Kripa E, Iannacone A, Orlandi M, Guarnieri V, Diacinti D, Minisola S. Imaging technologies in the differential diagnosis and follow-up of brown tumor in primary
hyperparathyroidism: case report and review of the literature. *Bone Rep*. 2020;30(14):100745.

261. Naswa N SP, Kumar A, Soundararajan, R, Kumar R, Malhotra A, Ammini AC, Bal C. ^{68}Ga-DOTANOC PET/CT in patients with carcinoma of unknown primary of neuroendocrine origin. *Clin Nucl Med*. 2012;37(3):245-51.

262. CuthbertsonDJ BJ, Lamarca A, Manoharan P, Westwood T, Jaffa M, Fenwick SW, Nuttall C, Lalloo F, Prachalias A, Pizanias M, Wieshmann H, McNamara MG, Hubner R, Srirajaskanthan R, Vivian G, Ramage J, Weickert MO, Pritchard DM, Vinjamuri S, Valle J, Yip VS. The Impact of 68Gallium DOTA PET/CT in Managing Patients With Sporadic and Familial Pancreatic Neuroendocrine Tumours. *Front Endocrinol*. 2021;12doi:10.3389/fendo.2021.654975

263. Kobayashi H, Makise N, Ito N, et al. Surgical margin for phosphaturic mesenchymal tumors in soft tissues: An analysis of the radiological histopathological correlation. *J Orthop Sci*. Sep 2021;26(5):870-877. doi:10.1016/j.jos.2020.07.006

264. Sun ZJ, Jin J, Qiu GX, Gao P, Liu Y. Surgical treatment of tumor-induced osteomalacia: a retrospective review of 40 cases with extremity tumors. *BMC Musculoskelet Disord*. Feb 26 2015;16:43. doi:10.1186/s12891-015-0496-3

265. Jiang Y, Li X, Huo L, et al. Consensus on clinical management of tumor-induced osteomalacia. *Chin Med J (Engl)*. Apr 1 2021;134(11):1264-1266. doi:10.1097/cm9.0000000000001448

266. Wang H, Zhong D, Liu Y, et al. Surgical Treatments of Tumor-Induced Osteomalacia Lesions in Long Bones: Seventeen Cases with More Than One Year of Follow-up. *J Bone Joint Surg Am*. Jul 1 2015;97(13):1084-94. doi:10.2106/jbjs.N.01299

267. Zhu W, Ma Q, Bian Y, et al. Total hip/knee arthroplasty in the treatment of tumor-induced osteomalacia patients: More than 1 year follow-up. *PLoS One*. 2017;12(5):e0177835. doi:10.1371/journal.pone.0177835

268. Ledford CK, Zelenski NA, Cardona DM, Brigman BE, Eward WC. The phosphaturic mesenchymal tumor: why is definitive diagnosis and curative surgery often delayed? *Clin Orthop Relat Res*. Nov 2013;471(11):3618-25. doi:10.1007/s11999-013-3178-1

269. Zuo QY, Wang H, Li W, et al. Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients. *BMC Musculoskelet Disord*. Sep 21 2017;18(1):403. doi:10.1186/s12891-017-1756-1

270. Chua SC, O'Connor SR, Wong WL, Ganatra RH. Case report: Solitary plasmacytoma of bone with oncogenic osteomalacia: recurrence of tumour confirmed by PET/CT. A case report with a review of the radiological literature. *Br J Radiol*. Apr 2008;81(964):e110-4. doi:10.1259/bjr/58168443

271. Dezfulian M, Wohlgenannt O. Revision hip arthroplasty following recurrence of a phosphaturic mesenchymal tumor. *J Surg Case Rep*. Sep 20 2013;2013(9)doi:10.1093/jscr/rjt059

272. Yasuda S, Wada S, Kono S, et al. Tumor-induced osteomalacia: benign tumor recurrence after two surgical resections at two different medical institutions. *Endocr Pract*. Jul-Aug 2013;19(4):e97-101. doi:10.4158/ep13042.Cr

273. Shi X, Jing H, Li F, Zhao Y, Wang Z, Huo L. 99mTc-HYNIC-TOC in the Evaluation of Recurrent Tumor-Induced Osteomalacia. *Clin Nucl Med*. Mar 2019;44(3):209-213. doi:10.1097/rlu.0000000000002458

274. Bhalla MI, Wirtz KM, Fair ES, Bucklan DJ. (68)Ga-DOTATATE positron emission tomography/computed tomography to detect the recurrence of phosphaturic mesenhcymal tumor-induced osteomalacia. *World J Nucl Med*. Jan-Mar 2020;19(1):78-81. doi:10.4103/wjnm.WJNM_92_18

275. Seijas R, Ares O, Sierra J, Pérez-Dominguez M. Oncogenic osteomalacia: two case reports with surprisingly different outcomes. *Arch Orthop Trauma Surg*. Apr 2009;129(4):533-9. doi:10.1007/s00402-008-0808-2

276. Aziz KT, McCarthy EF, Morris CD. Oncogenic Osteomalacia Secondary to a Metastatic Phosphaturic Mesenchymal Tumor in the Talus: A Case Report and Review of the Literature. *JBJS Case Connect*. Apr-Jun 2017;7(2):e40. doi:10.2106/jbjs.Cc.16.00172

277. Nair A, Chakraborty S, Dharmshaktu P, et al. Peptide Receptor Radionuclide and Octreotide: A Novel Approach for Metastatic Tumor-Induced Osteomalacia. *J Endocr Soc*. Jun 1 2017;1(6):726-730. doi:10.1210/js.2016-1088

278. Rai GS. Oncogenic osteomalacia associated with metastatic prostate carcinoma. *J Am Geriatr Soc*. Jun 1994;42(6):688. doi:10.1111/j.1532-5415.1994.tb06875.x

279. Goodwin CR, Clarke MJ, Gokaslan ZL, et al. En Bloc Resection of Solitary Functional Secreting Spinal Metastasis. *Global Spine J*. May 2016;6(3):277-83. doi:10.1055/s-0035-1558654

280. Reyes-Múgica M, Arnsmeier SL, Backeljauw PF, Persing J, Ellis B, Carpenter TO. Phosphaturic mesenchymal tumor-induced rickets. *Pediatr Dev Pathol*. Jan-Feb 2000;3(1):61-9. doi:10.1007/s100240050008

281. Luo L, Low N, Vandervord J. Mandibular phosphaturic mesenchymal tumor-mixed connective tissue variant in a young girl. *Cleft Palate Craniofac J*. Nov 2013;50(6):751-3. doi:10.1597/12-085

282. Farmakis SG, Siegel MJ. Phosphaturic mesenchymal tumor of the tibia with oncogenic osteomalacia in a teenager. *Pediatr Radiol*. Aug 2015;45(9):1423-6. doi:10.1007/s00247-015-3301-4

283. Fernández-Cooke E, Cruz-Rojo J, Gallego C, et al. Tumor-induced rickets in a child with a central giant cell granuloma: a case report. *Pediatrics*. Jun 2015;135(6):e1518-23. doi:10.1542/peds.2014-2218

284. Oyama N, Kojima-Ishii K, Toda N, et al. Malignant transformation of phosphaturic mesenchymal tumor: a case report and literature review. *Clin Pediatr Endocrinol*. 2020;29(2):69-75. doi:10.1297/cpe.29.69

285. Tantisattamo E, Ng RC. Dual paraneoplastic syndromes: small cell lung carcinoma-related oncogenic osteomalacia, and syndrome of inappropriate antidiuretic hormone secretion: report of a case and review of the literature. *Hawaii Med J*. Jul 2011;70(7):139-43.

286. Zheng G, Kanduri SR, Canterbury JP, Nguyen T, Velez JCQ. A Case of Hypophosphatemia due to Oncogenic Osteomalacia in a Patient with Natural Killer T-Cell Lymphoma. *Kidney Blood Press Res*. 2021;46(5):647-651. doi:10.1159/000516390

287. Feng J, Jiang Y, Wang O, Li M, Xia W-b. The diagnostic dilemma of tumor induced osteomalacia: A retrospective analysis of 144 cases. *Endocrine Journal*. 2017;64(7)

288. Kumar S, Diamond T. Lessons learnt from delayed diagnosis of FGF-23-producing tumour-induced osteomalacia and post-operative hungry bone syndrome. *Bone Rep*. Jun 2020;12:100276. doi:10.1016/j.bonr.2020.100276

289. Peacock M, Aaron JE, Heyburn PJ, Nordin BE. The action of 1alphahydroxy vitamin D3 and phosphate supplements in hypophosphataemic osteomalacia. *Adv Exp Med Biol*. 1977;81:431-40. doi:10.1007/978-1-4613-4217-5_44

290. Peacock M, Heyburn PJ, Aaron JE. Vitamin D resistant hypophosphataemic osteomalacia: treatment with 1alpha-hydroxyvitamin D3. *Clin Endocrinol (Oxf)*. Dec 1977;7 Suppl:231s-237s.

291. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol*. Jul 2019;15(7):435-455. doi:10.1038/s41581-019-0152-5

292. Liu S, Quarles LD. How fibroblast growth factor 23 works. *J Am Soc Nephrol*. Jun 2007;18(6):1637-47. doi:10.1681/ASN.2007010068

293. Lecoq AL, Chaumet-Riffaud P, Blanchard A, et al. Hyperparathyroidism in Patients With X-Linked Hypophosphatemia. *J Bone Miner Res*. Jul 2020;35(7):1263-1273. doi:10.1002/jbmr.3992

294. Brandi ML, Clunie GPR, Houillier P, et al. Challenges in the management of tumor-induced osteomalacia (TIO). *Bone*. Nov 2021;152:116064. doi:10.1016/j.bone.2021.116064

295. Geller JL, Khosravi A, Kelly MH, Riminucci M, Adams JS, Collins MT. Cinacalcet in the management of tumor-induced osteomalacia. *J Bone Miner Res*. Jun 2007;22(6):931-7. doi:10.1359/jbmr.070304

296. Bergwitz C, Collins MT, Kamath RS, Rosenberg AE. Case records of the Massachusetts General Hospital. Case 33-2011. A 56-year-old man with hypophosphatemia. *N Engl J Med*. Oct 27 2011;365(17):1625-35. doi:10.1056/NEJMcpc1104567

297. Seufert J, Ebert K, Muller J, et al. Octreotide therapy for tumor-induced osteomalacia. *N Engl J Med*. Dec 27 2001;345(26):1883-8. doi:10.1056/NEJMoa010839

298. Ovejero D, El-Maouche D, Brillante BA, Khosravi A, Gafni RI, Collins MT. Octreotide Is Ineffective in Treating Tumor-Induced Osteomalacia: Results of a Short-Term Therapy. *J Bone Miner Res*. Aug 2017;32(8):1667-1671. doi:10.1002/jbmr.3162

299. Jan de Beur SM, Miller PD, Weber TJ, et al. Burosumab for the Treatment of Tumor-Induced Osteomalacia. *J Bone Miner Res*. Apr 2021;36(4):627-635. doi:10.1002/jbmr.4233

300. Imanishi Y, Ito N, Rhee Y, et al. Interim Analysis of a Phase 2 Open-Label Trial Assessing Burosumab Efficacy and Safety in Patients With Tumor-Induced Osteomalacia. *J Bone Miner Res*. Feb 2021;36(2):262-270. doi:10.1002/jbmr.4184

301. Day AL, Gutiérrez OM, Guthrie BL, Saag KG. Burosumab in tumor-induced osteomalacia: A case report. *Joint Bone Spine*. Jan 2020;87(1):81-83. doi:10.1016/j.jbspin.2019.07.012

302. Oe Y, Kameda H, Nomoto H, et al. Favorable effects of burosumab on tumor-induced osteomalacia caused by an undetectable tumor: A case report. *Medicine (Baltimore)*. Nov 19 2021;100(46):e27895. doi:10.1097/md.0000000000027895

303. Miyaoka D, Imanishi Y, Yano M, et al. Effects of burosumab on osteocalcin and bone mineral density in patient with 15-year history of nonremission tumor-induced osteomalacia initially treated with conventional therapy: Case report. *Bone Rep*. Dec 2020;13:100736. doi:10.1016/j.bonr.2020.100736

304. Wöhrle S, Henninger C, Bonny O, et al. Pharmacological inhibition of fibroblast growth factor (FGF) receptor signaling ameliorates FGF23-mediated hypophosphatemic rickets. *J Bone Miner Res*. Apr 2013;28(4):899-911. doi:10.1002/jbmr.1810

305. Miller CB, Bergwitz C, Blau J, et al. Response of tumor-induced osteomalacia (TIO) to the FGFR inhibitor BGJ398. *Journal of Clinical Oncology*. 2016;34(15_suppl):e22500-e22500. doi:10.1200/JCO.2016.34.15_suppl.e22500

306. Hartley IR, Miller CB, Papadakis GZ, et al. Targeted FGFR Blockade for the Treatment of Tumor-Induced Osteomalacia. *N Engl J Med*. Oct 1 2020;383(14):1387-1389. doi:10.1056/NEJMc2020399

307. Hesse E, Rosenthal H, Bastian L. Radiofrequency ablation of a tumor causing oncogenic osteomalacia. *N Engl J Med*. Jul 26 2007;357(4):422-4. doi:10.1056/NEJMc070347

2464 308. Xian MF, Pan KM, Zhang JC, et al. Application of ultrasound-guided biopsy and percutaneous
2465 radiofrequency ablation in 2 cases with phosphaturic mesenchymal tumor and literature review. *Clin Hemorheol*
2466 *Microcirc*. 2021;77(1):61-69. doi:10.3233/ch-200921
2467 309. Maybody M, Grewal RK, Healey JH, et al. Ga-68 DOTATOC PET/CT-Guided Biopsy and
2468 Cryoablation with Autoradiography of Biopsy Specimen for Treatment of Tumor-Induced Osteomalacia.
2469 *Cardiovasc Intervent Radiol*. Sep 2016;39(9):1352-7. doi:10.1007/s00270-016-1350-1
2470 310. Tella SH, Amalou H, Wood BJ, et al. Multimodality Image-Guided Cryoablation for Inoperable Tumor-
2471 Induced Osteomalacia. *J Bone Miner Res*. Nov 2017;32(11):2248-2256. doi:10.1002/jbmr.3219
2472 311. Igney-Oertel A, Artunc F, Henes J, Hoffmann R, Clasen S. Osteomalacia by a mesenchymal-FGF23-
2473 producing tumour: Successful treatment with radiofrequency ablation. A case report. *Joint Bone Spine*. Oct
2474 2016;83(5):603-4. doi:10.1016/j.jbspin.2015.09.011
2475 312. Horng JC, Van Eperen E, Tutton S, Singh R, Shaker JL, Wooldridge AN. Persistent phosphaturic
2476 mesenchymal tumor causing tumor-induced osteomalacia treated with image-guided ablation. *Osteoporos Int*. Sep
2477 2021;32(9):1895-1898. doi:10.1007/s00198-020-05795-1
2478 313. Jadhav S, Kasaliwal R, Shetty NS, et al. Radiofrequency ablation, an effective modality of treatment in
2479 tumor-induced osteomalacia: a case series of three patients. *J Clin Endocrinol Metab*. Sep 2014;99(9):3049-54.
2480 doi:10.1210/jc.2013-4515
2481 314. Cowan S, Lozano-Calderon SA, Uppot RN, Sajed D, Huang AJ. Successful CT guided cryoablation of
2482 phosphaturic mesenchymal tumor in the soft tissues causing tumor-induced osteomalacia: a case report. *Skeletal*
2483 *Radiol*. Feb 2017;46(2):273-277. doi:10.1007/s00256-016-2548-7
2484 315. Mishra SK, Kuchay MS, Sen IB, Garg A, Baijal SS, Mithal A. Successful Management Of Tumor-
2485 Induced Osteomalacia with Radiofrequency Ablation: A Case Series. *JBMR Plus*. Jul 2019;3(7):e10178.
2486 doi:10.1002/jbm4.10178
2487 316. Tutton S, Olson E, King D, Shaker JL. Successful treatment of tumor-induced osteomalacia with CT-
2488 guided percutaneous ethanol and cryoablation. *J Clin Endocrinol Metab*. Oct 2012;97(10):3421-5.
2489 doi:10.1210/jc.2012-1719
2490 317. Sorbye H, Kong G, Grozinsky-Glasberg S. PRRT in high-grade gastroenteropancreatic neuroendocrine
2491 neoplasms (WHO G3). *Endocr Relat Cancer*. Mar 2020;27(3):R67-r77. doi:10.1530/erc-19-0400
2492 318. Basu S, Fargose P. 177Lu-DOTATATE PRRT in Recurrent Skull-Base Phosphaturic Mesenchymal
2493 Tumor Causing Osteomalacia: A Potential Application of PRRT Beyond Neuroendocrine Tumors. *J Nucl Med*
2494 *Technol*. Dec 2016;44(4):248-250. doi:10.2967/jnmt.116.177873
2495 319. Tarasova VD, Trepp-Carrasco AG, Thompson R, et al. Successful treatment of tumor-induced
2496 osteomalacia due to an intracranial tumor by fractionated stereotactic radiotherapy. *J Clin Endocrinol Metab*. Nov
2497 2013;98(11):4267-72. doi:10.1210/jc.2013-2528
2498 320. Massaccesi M, Miccichè F, Rigante M, et al. Successful Treatment of Tumor-Induced Osteomalacia by
2499 Multidisciplinary Therapy with Radiation to Intracranial Fibromyxoid Tumor. *Case Rep Endocrinol*.
2500 2021;2021:8841259. doi:10.1155/2021/8841259
2501 321. Fuentealba C, Pinto D, Ballesteros F, et al. Oncogenic hypophosphatemic osteomalacia associated with
2502 a nasal hemangiopericytoma. *J Clin Rheumatol*. Dec 2003;9(6):373-9. doi:10.1097/01.rhu.0000101906.15276.ed
2503 322. Peters KB, McLendon R, Morse MA, Vredenburgh JJ. Treatment of Recurrent Intracranial
2504 Hemangiopericytoma with SRC-Related Tyrosine Kinase Targeted Therapy: A Case Report. *Case Rep Oncol*. Apr
2505 8 2010;3(1):93-97. doi:10.1159/000307468

323. Corsi A, Boldrini R, Bosman C. Congenital-infantile fibrosarcoma: study of two cases and review of the literature. *Tumori*. Oct 31 1994;80(5):392-400.

LEGENDS TO FIGURES

Figure 1. Interactions between FGF23, vitamin D and parathyroid hormone. Fibroblast growth factor 23 (FGF23), produced by osteocytes and osteoblasts exerts its effects on the kidney and negatively affects parathyroid hormone (PTH) secretion. As a consequence there is a decrease in Cyp27b1 activity and 1,25(OH)2D production. The final cumulative net effect is a reduction of circulation serum phosphate values. NaPi-2a and 2c refer to sodium dependent phosphate transport protein 2a and 2c, respectively. Red arrows refer to the actions of PTH. Values of PTH are not suppressed, because there is also a stimulatory effect consequent to deficient calcium absorption.

Figure 2. Proposed mechanisms of FGF23 overproduction and actions of FGF23

Fibronectin (FN1)-FGFR1 or *FN1-FGF1* fusion gene has been reported in tumors responsible for TIO. FN1-FGFR1 fusion protein is considered to facilitate the activation of FGFR1. FN1-FGF1 fusion protein is proposed to be secreted and bind to FGFR1. Ectopic expression of KLOTHO makes the cells responsive to FGF23. All these mechanisms lead to activation of FGFR1 and may be involved in the overproduction of FGF23. These three abnormalities have been reported to be mutually exclusive. FGF23 then binds to KLOTHO-FGFR1 complex in

target cells. FGF23 suppresses the expression of type 2a and 2c sodium-phosphate cotransporters and inhibits proximal tubular phosphate reabsorption. FGF23 also suppresses the expression of *CYP27B1* and enhances that of *CYP24A1* thereby reducing $1,25(OH)_2D$ level and intestinal phosphate absorption.

Figure 3. Two PMTs involving the soft tissues of the left groin and the head of the right femur [117] are illustrated in a and b, respectively. Hemorrhages (arrows) are recognizable in the soft tissue tumor. The color of the bone tumor (asterisk) is brownish for the high vascularization. Bar in a and b: cm 2.

Figure 4. Representative histological images of PMTs. These tumors consist of bland, round-ovoidal cells associated with florid vascularization which include variable sized blood-vessels ranging from slit “hemangiopericytoma-like” (a) to large cavernous spaces (b). The florid vasculature is highlighted by CD34 immunostain (c). A more compact and densely cellular area is illustrated in d while an area with an overt excess of extracellular matrix (asterisk) is shown in e. Calcifications of the extracellular matrix are shown in f (arrows) and g (asterisks). The amount of matrix calcification is commonly smaller in sinonasal PMTs compared to those occurring in soft tissues and bones. Mature adipocytes (*ad* in f) are more frequently found in PMTs involving the sinonasal

region while multinucleated giant-cells (h) are virtually a constant finding in those involving soft tissues and bones. As osteoclasts, multinucleated giant-cells are positive for TRAP (insert in h, red staining). The image in i illustrates a section obtained from a bone PMT processed for plastic embedding and stained with von Kossa [117]. A thick osteoid seam (unstained in black with von Kossa, asterisk), indicating osteomalacia, is evident in an intra-tumoral bone trabecula. Panels a, b, and g-i: bone PMT. Panels c and d; sinonasal PMT. Panels e and f: soft tissue PMT. Panels a, b and d-h: haematoxylin-eosin. Panel c: CD34 immunostaining. Insert in panel h: TRAP staining. Panel i: von Kossa-methylene blue staining. Bar in a-c, e and f: 200 µm. Bar in d and h: 100 µm. Bar in g and i: 120 µm. Bar in the insert in h: 60 µm. In i, PMT is for Phosphaturic Mesenchymal Tumor.

Figure 5. High power histological images of PMT-cells and mineralization of the intra-tumoral extracellular matrix are illustrated in a and b, respectively. Panels c-e were generated from samples of two PMTs, one in bone and the other in the soft tissues, processed for Transmission Electron Microscopy [323]. A typical PMT cell is shown in c. It shows irregular nucleus, inconspicuous nucleolus, some mitochondria, cisternae of rough endoplasmic reticulum and small vesicles. The mineral deposits in the extracellular matrix are illustrated in d (asterisk). They appear to be in intimate association with an individual

tumor cell. The panel e shows intra-cytoplasmic dense core membrane bound neurosecretory-like granules, one of which is highlighted in the insert. Panels a and c: bone PMT. Panels b, d and e; soft tissue PMT. Panels a and b: hematoxylin-eosin. Panels c-e: lead citrate-uranyl acetate. Bar in a and b: 30 µm. Bar in c and d: 1 µm. Bar in e: 300 nm. Bar in the insert in e: 150 nm.

Figure 6. Diagnostic algorithm of the evaluation of suspected TIO. SPECT, single-photon emission computed tomography; CT, computed tomography; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; ^{18}FDG PET-CT, fluorodeoxyglucose positron emission tomography-CT; MRI, magnetic resonance imaging

Figure 7. Mechanism of actions for the existing and potential novel therapies. The tumor cell secretes fibroblast growth factor 23 (FGF23), which promotes renal phosphate excretion and reduces $1,25(OH)_2D$ concentrations, by inhibiting sodium-dependent phosphate transport protein 2A and 2C (NPT2A and NPT2C) and cytochrome P450 family 27 subfamily B member 1 (CYP27B1), while stimulating cytochrome P450 family 24 subfamily A member 1 (CYP24A1) on tubule cells, via fibroblast growth factor receptor 1 (FGFR1). On the other side, parathyroids secrete parathyroid hormone (PTH), which also downregulates NPT2A and NPT2C, but has opposite effects on CYP27B1 and

CYP24A1 compared with FGF23. $1,25(OH)_2D$ stimulates phosphate absorption in the intestine. Surgery, ablation, radiotherapy and peptide receptor radionuclide therapy (PPRT) are therapies aiming to eliminate tumor cells. Octreotide binds to somatostatin 2A, 2B and 5 (SSTR2A/2B/5) on the tumor cell, thereby reduces the secretion of FGF23 in some cases. The novel therapies including FGF23 antibodies and FGFR inhibitors suppress the effect of FGF23 by binding to FGF23 itself or FGFR1, respectively. Cinacalcet, a positive allosteric modulator (PAM) of the calcium-sensing receptor (CaSR), acts on parathyroid to reduce the release of PTH. Conventional medical therapy comprises oral preparations of phosphate and an active vitamin preparation (e.g., calcitriol or alfacalcidol).

2606

2607 **Table 1. Differential diagnosis of TIO**

Condition	Common clinical features	Common laboratory findings	Determinants of the differential diagnosis
TIO	Musculoskeletal pain, muscle weakness, skeletal deformities, height loss, difficulty to walking, disability, fractures	Hypophosphatemia; TRP < 85-95%, low TmP/GFR	-Clinical: age, family history, exclusion iatrogenic causes -Laboratory: high FGF 23
-Other musculoskeletal disorders (eg Paget, myopathy, etc) -Rheumatological, neurological and psychiatric disease	Musculoskeletal pain, muscle weakness, skeletal deformities, height loss, difficulty to walking, disability, fractures	-Paget: elevated serum ALK	Normal phosphate levels
Malabsorption syndrome	Musculoskeletal pain, muscle weakness, height loss, difficulty to walking, fractures	Hypocalcemia, hypophosphatemia, low serum 25(OH)D, elevated serum PTH and alkaline phosphatase	-Clinical: diarrhea, constipation, abdominal pain, weight loss, etc. -Laboratory: anemia, hypoalbuminemia, low ferritin; TRP ≥ 85-95%, normal TmP/GFR
-Nutritional phosphate deficiency -Vitamin D deficiency	Musculoskeletal pain, muscle weakness, skeletal deformities, height loss, difficulty to walking, disability, fractures	Hypocalcemia, hypophosphatemia, low serum 25(OH)D, elevated serum PTH and alkaline phosphatase	-Low dietary phosphate intake -Low or absent sun exposure -Laboratory: TRP ≥ 85-95%, normal TmP/GFR
Fanconi sydrome	Musculoskeletal pain, muscle weakness, height loss, difficulty to walking, fractures	Hypophosphatemia; TRP < 85-95%, low TmP/GFR	-Clinical: exposure to heavy metals, infections, light chain deposition disease, amyloidosis or other cause of acute tubular necrosis -Laboratory: low FGF23; metabolic acidosis; increased urinary bicarbonate, uric acid,

			glucose, amino acid, sodium, potassium, beta2-microglobulin and immunoglobulin
HHRH	Musculoskeletal pain, muscle weakness, skeletal deformities, height loss, difficulty to walking, disability, fractures	Hypophosphatemia; TRP < 85-95%, low TmP/GFR	-Clinical: young age; positive family history -Laboratory: high urinary calcium; low FGF23 -Genetic testing: SLC34A3
XLH, ADHR and ARHR	Musculoskeletal pain, muscle weakness, skeletal deformities, height loss, difficulty to walking, disability, fractures	Hypophosphatemia; TRP < 85-95%, low TmP/GFR	-Clinical: young age; growth retardation, bowing, dental and ear abnormalities; positive family history -Genetic testing: PHEX (XLH), FGF23 (ADHR), DMP1 (ARHR type 1), ENPP1 (ARHR type 2)
PFD/MAS	Musculoskeletal pain, muscle weakness, skeletal deformities, fractures	Hypophosphatemia; TRP < 85-95%, low TmP/GFR	-Clinical: typical bone lesions; coxa vara, scoliosis, facial deformity, vision or hearing loss; in MAS: cafe´-au-lait spots, precocious puberty, Leydig cell hyperplasia, thyroid abnormalities, GH excess -Radiology (X-ray, CT, MRI): focal lytic, mixed (ground-glass) or sclerotic lesions -Genetic testing: GNAS1
CSHS, OGD and HRH	Musculoskeletal pain, muscle weakness, skeletal deformities, height loss, difficulty to walking, disability, fractures	Hypophosphatemia; TRP < 85-95%, low TmP/GFR	-Clinical: young age (all); diffuse epidermal or melanocytic nevi (CSHS); craniofacial and teeth abnormalities, dwarfism (OGD) -Laboratory: high Klotho and PTH -Genetic testing: RAS (CSHS), FGFR1 (OGD)

TIO, tumor-induced osteomalacia; TRP , tubular reabsorption of phosphate; TmP/GFR, maximum tubular reabsorption of phosphate/glomerular filtration rate; FGF 23, fibroblast growth factor 23; ALK, phosphatase; 25(OH)D, 25-hydroxy-vitamin D; PTH, parathyroid hormone; HHRH, Hereditary hypophosphatemic rickets with hypercalciuria; XLH, X-Linked hypophosphatemia, ADHR autosomal dominant hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; PHEX, phosphate-regulating endopeptidase homolog X-linked; DMP1, dentin matrix acidic phosphoprotein 1;

2614 ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; CT, computed tomography; MRI, magnetic resonance imaging;
2615 PFD/MAS: Polyostotic Fibrous Dysplasia/McCune-Albright Syndrome; GH, growth hormone; CSHS, cutaneous skeletal
2616 hypophosphatemia syndrome; OGD, osteoglophonic dysplasia; HRH, hypophosphatemic rickets with hyperparathyroidism
2617

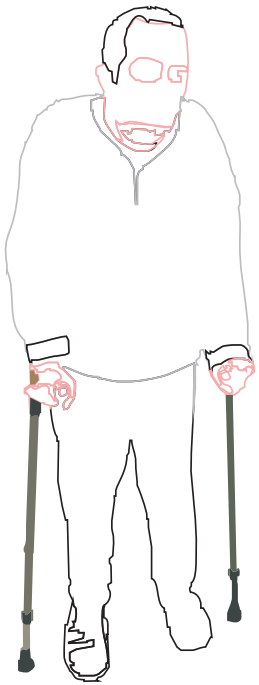
2618

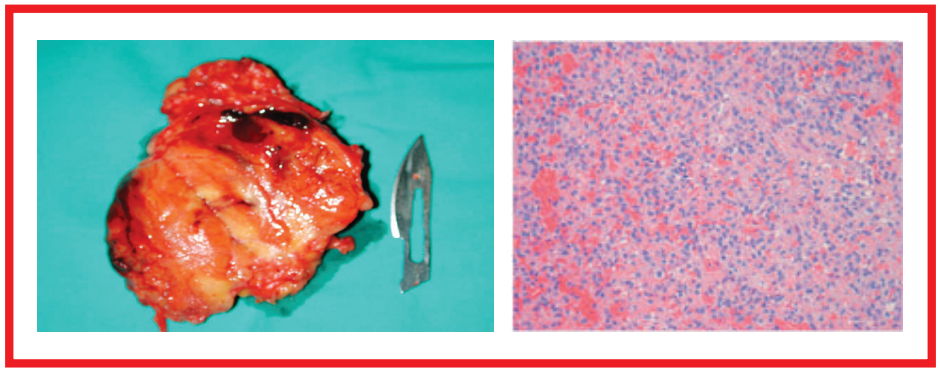
Table 2. Present and future therapies for TIO

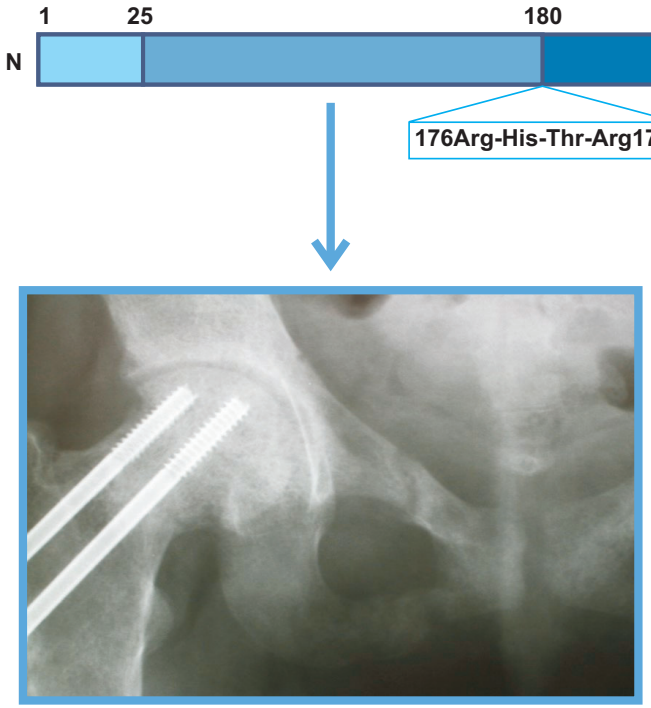
Treatment	Specific methods	Suitable group	Treatment outcome	Challenges
Surgery	Resection; Curettage; Injection of bone cement; Joint arthroplasty.	Patient with specific culprit tumor and complete resection is possible.	Complete tumor resection is the only definitive treatment. Serum phosphate and FGF23 concentrations usually normalized in several days. BMD significant increases within 2 -4 years.	The incidence of refractory varies from 0% to 57 % [9-22]. The outcome of surgical treatment largely depends on the site of culprit tumor and experience of the surgeon. Loss of some limb function and prosthesis related problems. Hungry bone disease [52].
Conventional medical treatment	20-40mg/kg/d for element phosphate (1 -3 g/d for adults) and 20 - 30ng/kg/d for calcitriol (0.5-1.5μg/d for adults) [6].	When the causative tumors are unresectable, multifocal, unlocalized, or complete resection is not possible.	Partially restore phosphate and vitamin D homeostasis, alleviate the symptoms and normalize bone mineralization	Several complications including nephrolithiasis, nephrocalcinosis, reduced kidney function, and hyperparathyroidism [9,49,55]. Achieving the b alance between optimizing clinical improvement and minimizing treatment complications.
FGF23 antibodies	Burosumab (0.3mg/kg to 2.0mg/kg every 4 weeks) [63-67].	Uncertain	Serum phosph ate and TmP/GFR level rapidly increased above the lower limit of normal and remained through the study course for 144 weeks. Bone histomorphometry parameters and self - reported symptoms improved. Approximately 50% of fractures/pseudofractures were at least partially healed by week 96.	The potential impact on tumor progre ssion is of concern.
FGFR Inhibitors	BGJ398 [71,72]. .	Uncertain	Normalization of FGF23 and phosphorus levels and tumor differentiation and osseous metaplasia.	Tyrosine kinase inhibitor-related side effects.
Other treatment	Radiotherapy; Image-guided Ablation; PPRT; Cinacalcet [18,41,59,60]; Octreotide [61,62].	Uncertain	Symptoms and biochemical abnormalities resolved completely or partially according to limited case reports.	The long-term effectiveness is uncertain.

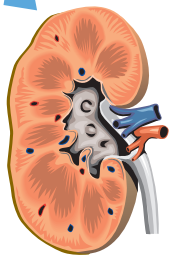
2619

Graphical Abstract









1 25 180 251

N C

176Arg-His-Thr-Arg179

Tumor removal

Full recovery

Decreased Phosphate Reabsorption

Figure 1

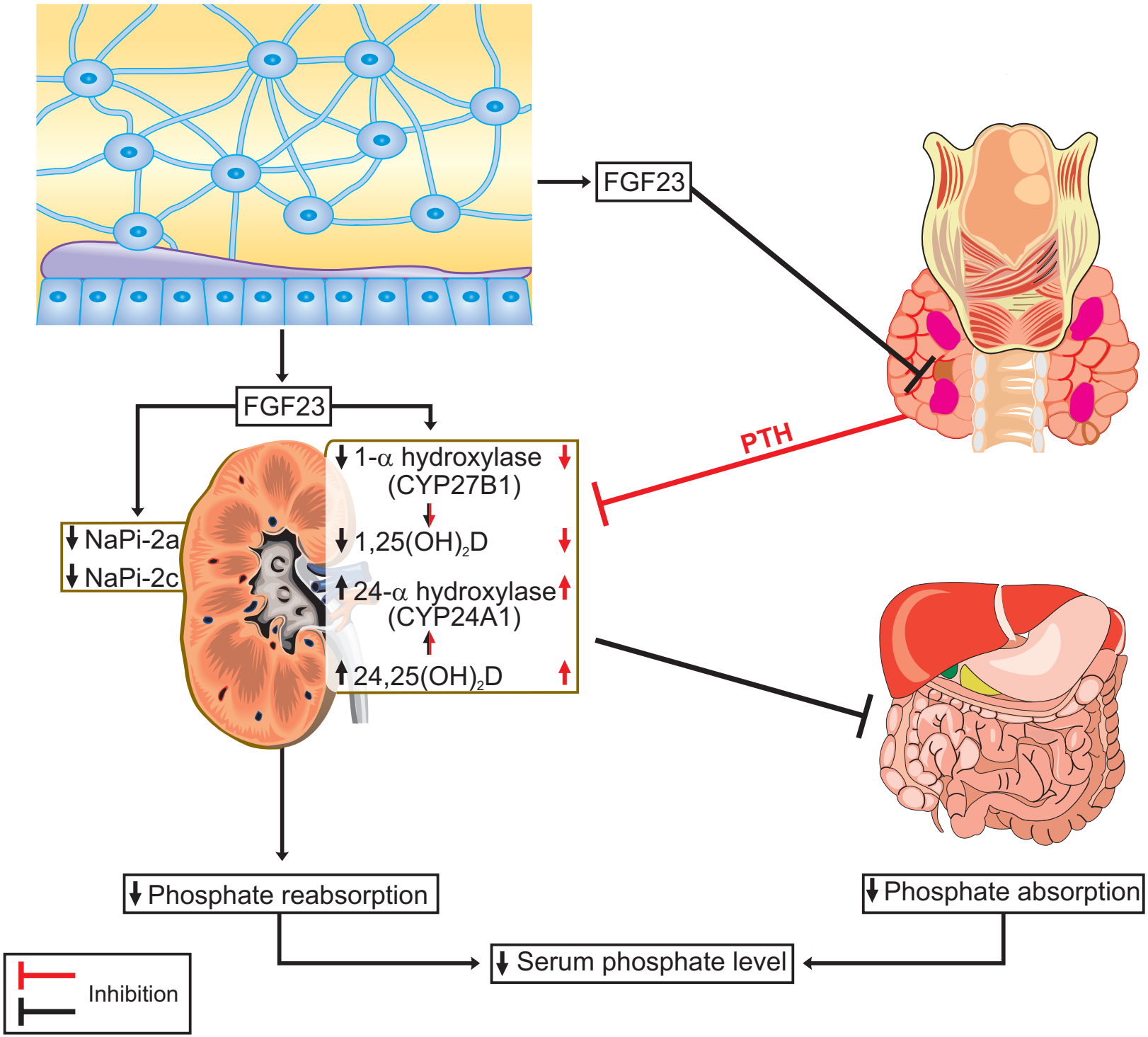


Figure 2

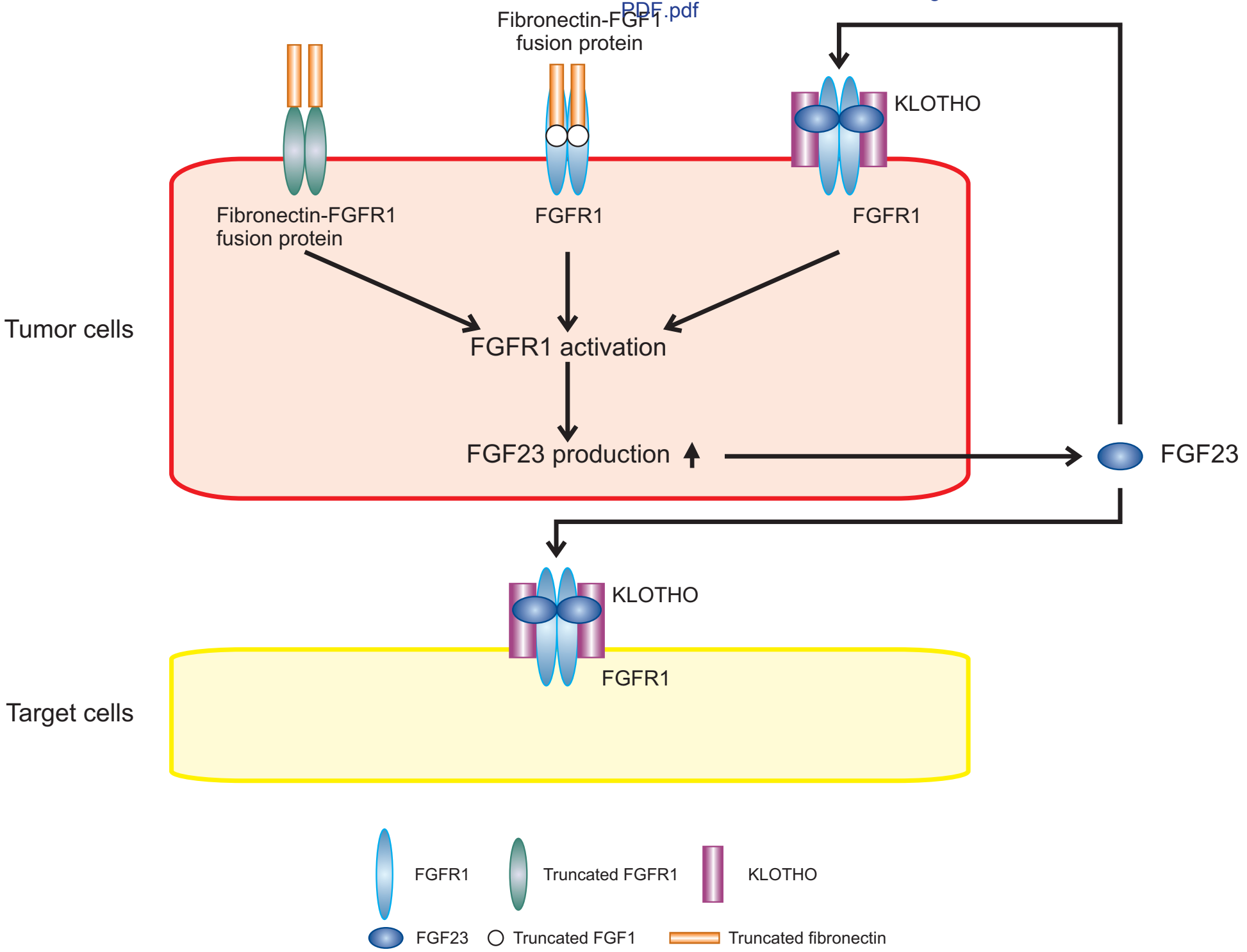


Figure 3

Click here to access/download;Figure;MI

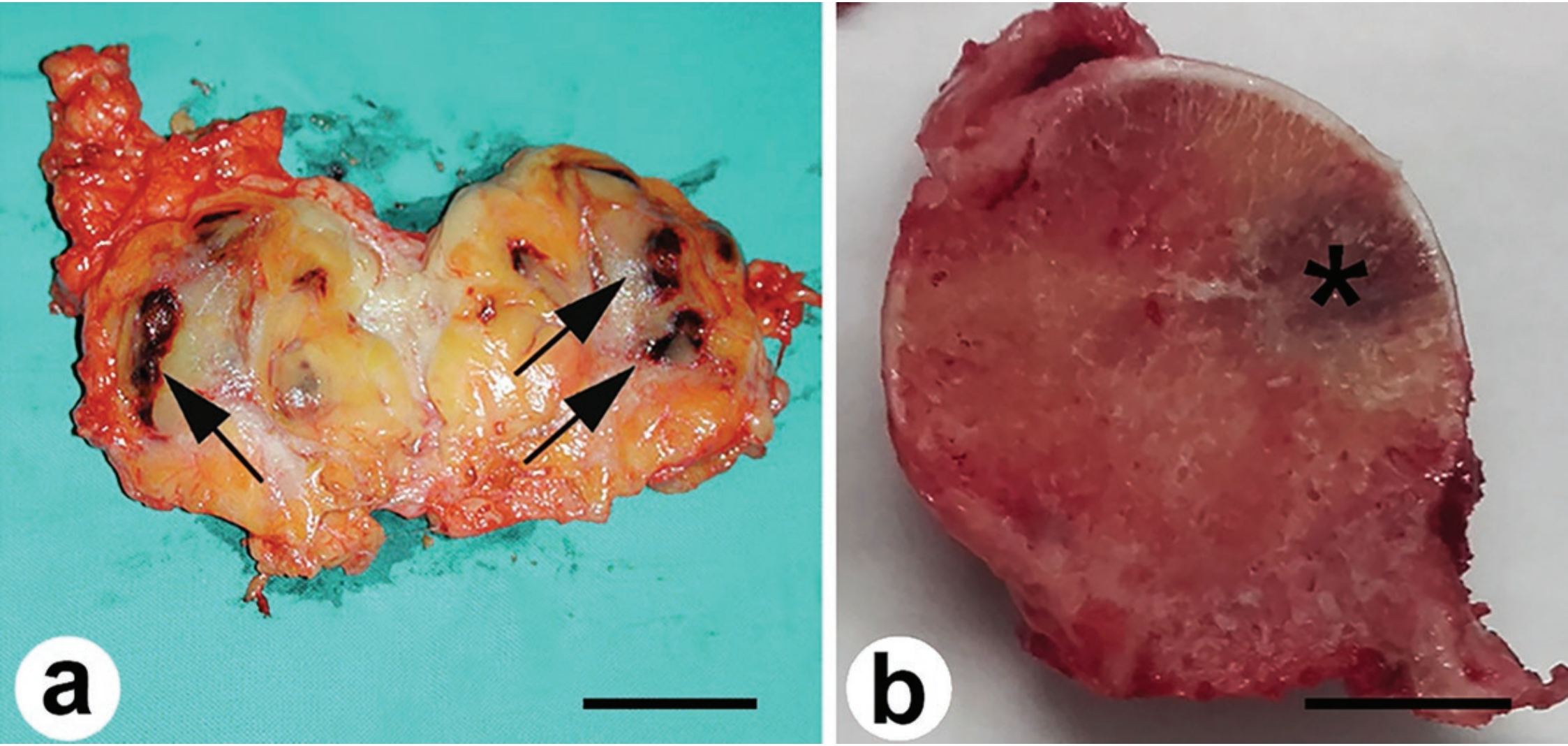


Figure 4

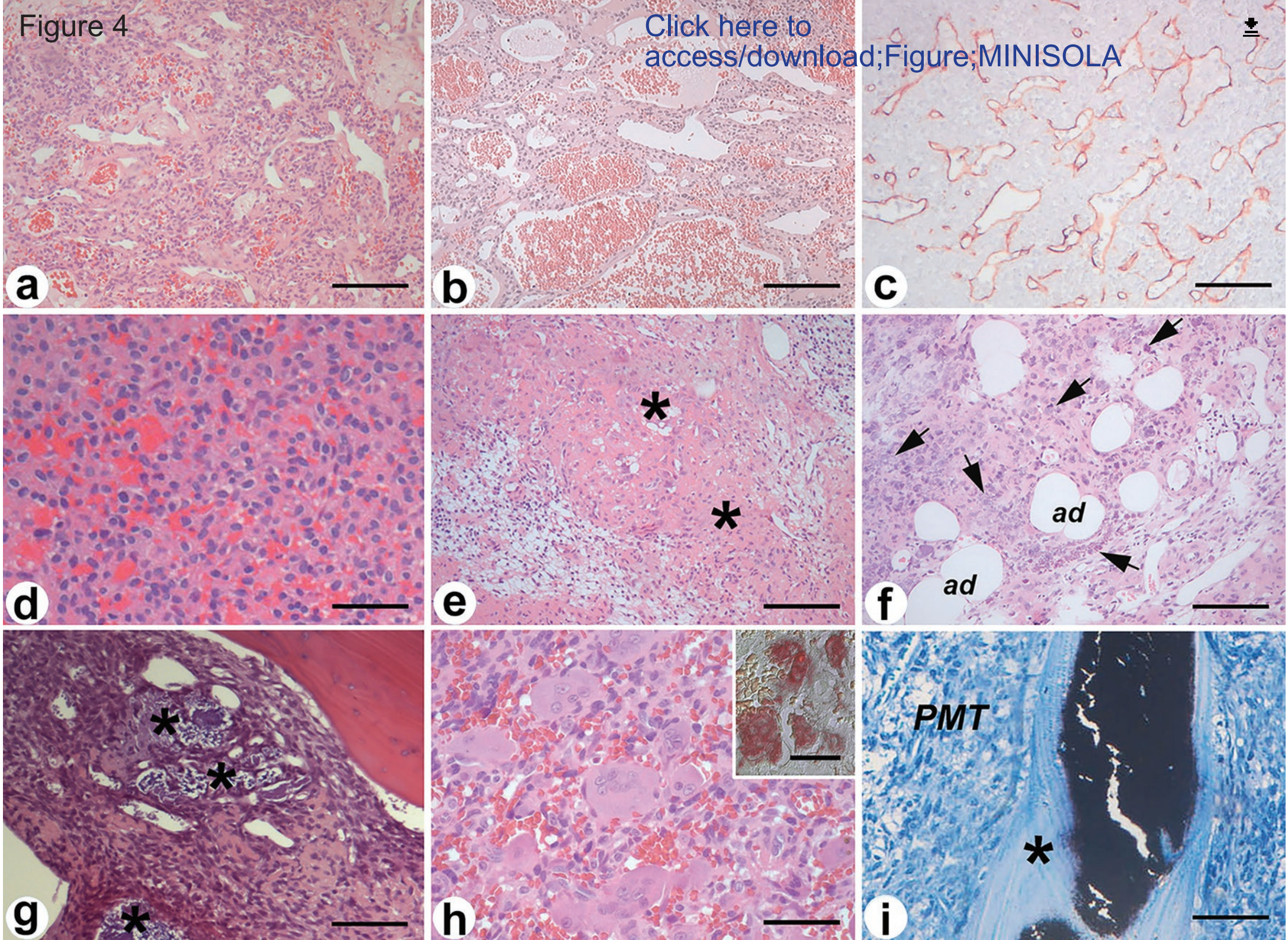


Figure 5

Click here to access/download;Figure;MINISOLA

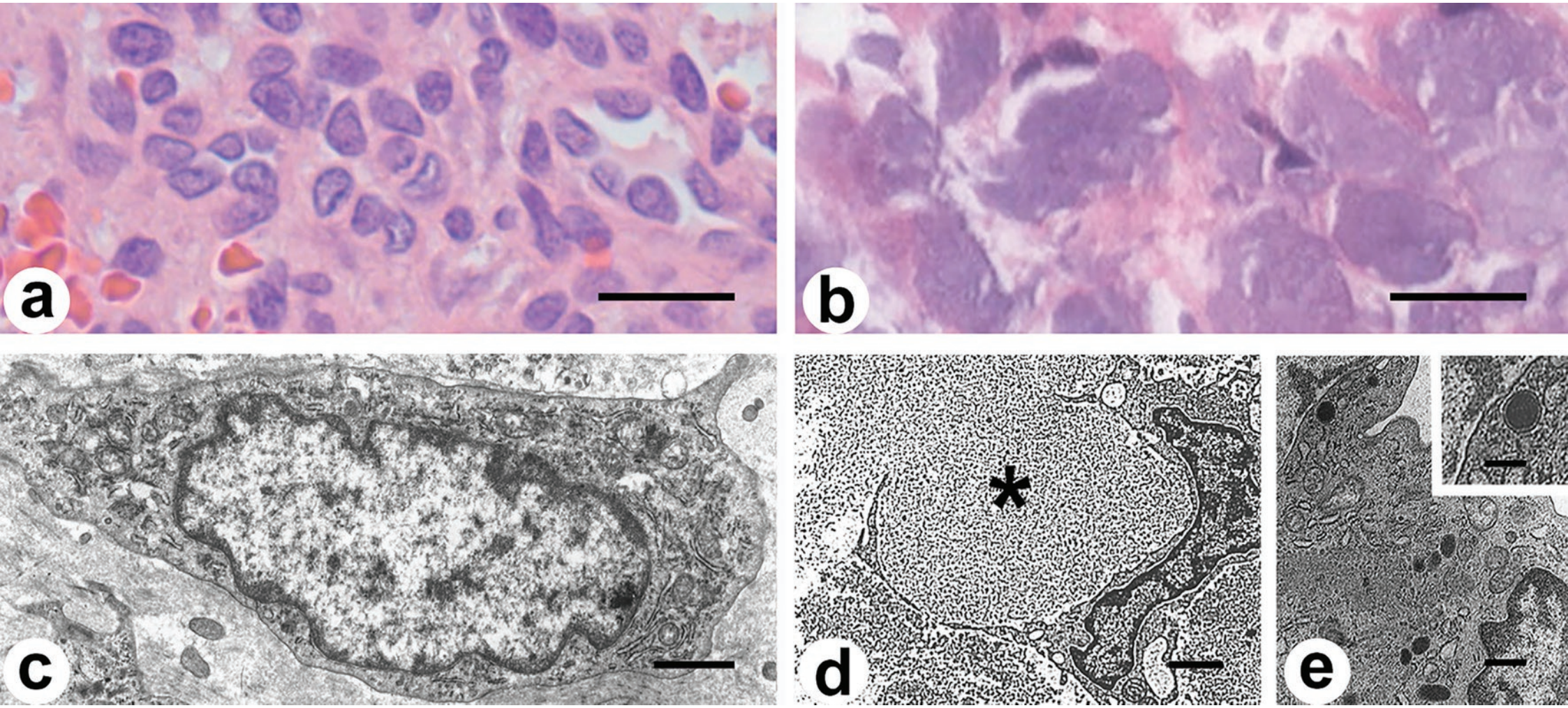


Figure 6

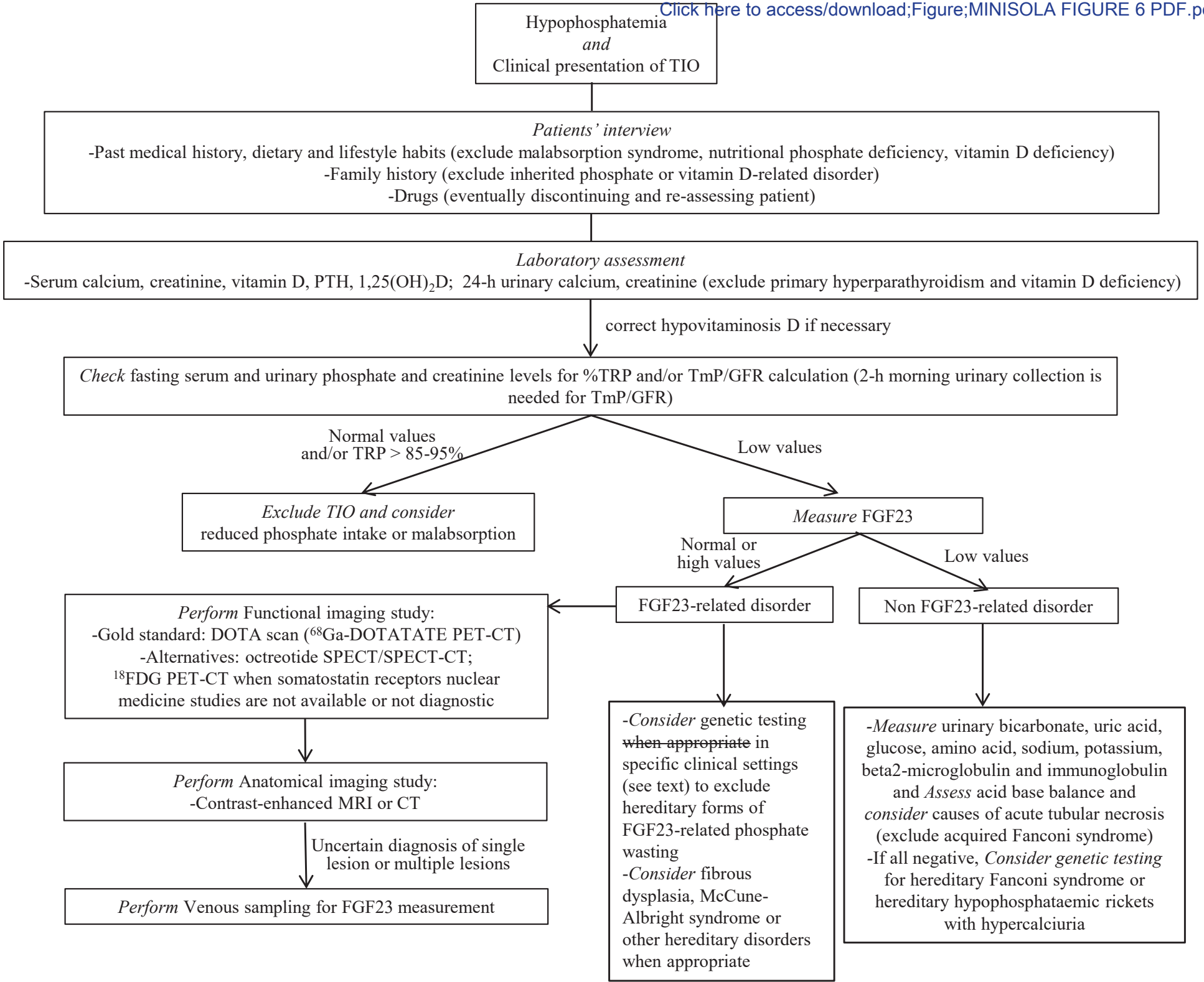
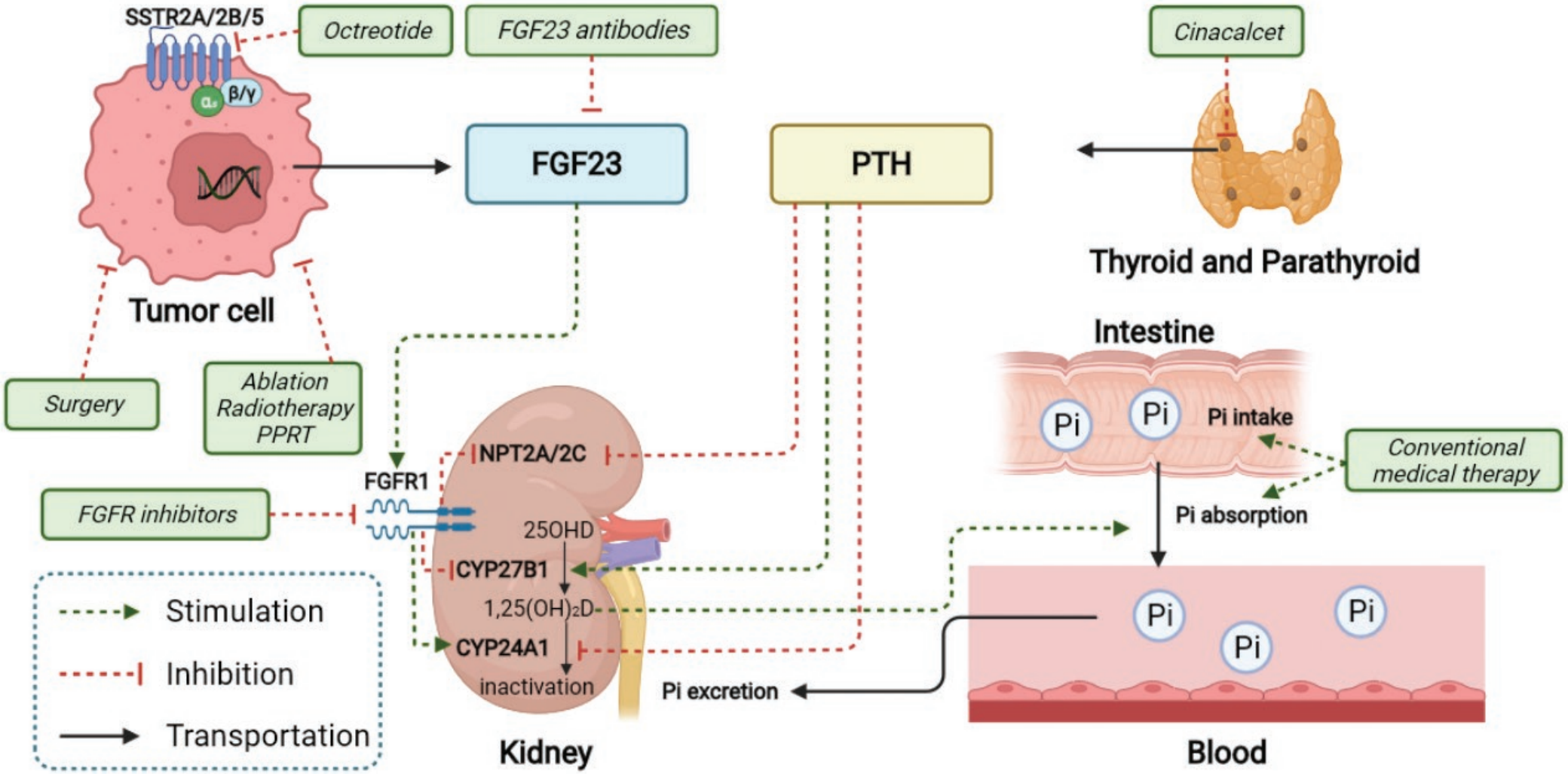


Figure 7

Click here to access/download;Figure;MINISOLA FIGURE 7 PDF.pdf



ESSENTIAL POINTS

1) Tumor induced osteomalacia is a paraneoplastic syndrome due to overproduction of fibroblast growth factor 23 (FGF23), which can severely impair morbidity of the affected patients.
2) Phosphaturic mesenchymal tumors are the pathological entities underlying tumor induced osteomalacia in most affected patients.
3) Biochemical features of tumor induced osteomalacia are represented by hypophosphatemia, increased or inappropriately normal levels of FGF23 and low to low normal circulating $1,25(OH)_2D$.
4) Tumor induced osteomalacia is an underdiagnosed disease, whose awareness should be increased among physicians, for timely and proper management of the patients
5) There is now evidence that FN1-FGFR1 and FN1-FGF1 fusion genes are present in about half of tumors causing this paraneoplastic syndrome.
6) There are a number of function and anatomical imaging techniques utilized for tumor localization; ^{68}Ga DOTA based technologies have the better sensitivity.
7) Surgery is the treatment of choice; several medical treatments are now available in case of inability to locate the tumor or in case of incomplete excision.